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Evidence for Whom? A Systematic Review of Eligibility Criteria in RCTs of Anti-VEGF for Neovascular Age-Related Macular Degeneration

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ABSTRACT

Purpose: To summarize the eligibility criteria used in randomized controlled trials (RCT) of intravitreal anti-VEGF treatments for neovascular age-related macular degeneration (AMD).
Design: Systematic review.
Methods: A search of 12 literature databases was conducted on 15 April 2024. RCTs of intravitreal anti-VEGF for the treatment of neovascular AMD in treatment-naïve eyes were identified. Data on the eligibility criteria for visual function, disease definition and stage, ocular comorbidities, systemic comorbidities, demographics, and other factors not included in other categories were extracted.
Results: A total of 49 eligible studies were included in this review, which together included 26,995 eyes of 26,995 patients. We identified a range of eligibility criteria on areas of visual function (minimum 18–50 ETDRS letters; maximum 69–78 ETDRS letters), disease definition and stage (FA only vs. multimodal approach), ocular and systemic comorbidities (most frequent exclusion criteria across studies were any history of the following: intraocular surgery, diabetic retinopathy, panretinal photocoagulation, glaucoma, and myopia), demographics, as well as a miscellaneous category with other topics. Studies employed a set of criteria so stringent that it could be questioned to which extent patients included were generalizable to real-world patients with AMD.
Conclusions: RCTs of anti-VEGF treatments for neovascular AMD employ stringent eligibility criteria, which in consequence may reduce the generalizability of findings to real-world populations.

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TABLE OF CONTENTS STATEMENT

To guide real-world clinical practice, evidence must be generalizable to real-world patients. However, many randomized clinical trials are specifically designed for approval purposes, and not necessarily with generalizability in mind. This review systematically examines the eligibility criteria in randomized clinical trials evaluating the use of anti-VEGF therapy for neovascular age-related macular degeneration. We find that these studies employ stringent eligibility criteria, which in consequence may reduce the generalizability of findings to real-world populations.

Introduction

Neovascular age-related macular degeneration (nAMD) is one of the leading causes of visual impairment in the developed world[1]. The development of nAMD is characterized by vascular endothelial growth factor (VEGF) expression that drives the development of macular neovascularization (MNV), leading to exudation and hemorrhage that can be symptomatic[2,3]. The introduction of anti-VEGF therapy has drastically improved the prognosis[4].

The intravitreal anti-VEGF drug ranibizumab (Lucentis, Novartis, Basel, Switzerland) was approved for use for nAMD in 2006 by the FDA and soon after there was a global adaptation of its use[5,6]. Its introduction was preceded by pivotal randomized clinical trials (RCTs), specifically the MARINA and ANCHOR phase 3 studies[7,8]. Since then, many other anti-VEGF drugs have been approved. The approval process is based on large RCTs, which document the drug efficacy when used as recommended. However, these studies not only serve a purpose of regulatory approval but also guide expectations for efficacy and prognosis in real-world clinical practice.

To guide real-world clinical practice, evidence must be generalizable to real-world patients. However, many RCTs are specifically designed for approval purposes, and not necessarily with generalizability in mind. Another aspect is the need to show good results of a new drug for the purpose of promotion and advertisement, which may also influence the design of the studies and their study population. This review aims to systematically examine the eligibility criteria in RCTs evaluating the use of anti-VEGF therapy for nAMD. The objective is to summarize and analyze the patient populations to which the findings of these RCTs can be generalized.

Methods

This study was a systematic review based on the recommendations of the Cochrane Handbook[9] and registered in the PROSPERO database (jr. no. CRD42024626918). Dissemination was made following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10].

Eligibility Criteria and Outcomes of Interest

Eligible studies fulfilled the following criteria:

Population: Patients at the age of $\geq$ 50 years with an nAMD diagnosis undergoing intravitreal anti-VEGF therapy. Patients of interest were those who were treatment-naïve and had not previously received any intravitreal anti-VEGF therapy, i.e., other types of therapies were not considered within this definition regardless of their proven or assumed efficacy. No restrictions were made on patient characteristics (e.g., age, sex, race) or any eye characteristics (e.g. phakic/pseudophakic, comorbidities, visual acuity). No restrictions based on subtypes of nAMD (i.e. type 1 macular neovascularisation (MNV), type 2 MNV, type 3 MNV) were made. However, studies with a substantial proportion of individuals with MNV due to other causes (myopic MNV, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy, inflammatory MNV, etc.) were not considered for this review. No restrictions on the anti-VEGF drug employed were imposed; however, any agents not considered routine intravitreal anti-VEGF therapy (at the discretion of the authors of this study) was not considered eligible for this study (e.g., port delivery devices, experimental delivery systems, implant-based systems). Intravitreal therapies other than anti-VEGF (e.g. antibiotics or corticosteroids) were not considered eligible for this study. No restrictions on the dosing regimen or loading phase were enforced, but such details were noted for the qualitative review.

Intervention and Comparison: Intravitreal injection using any anti-VEGF therapy. Comparison groups were defined as any other anti-VEGF treatment or no active treatment. Studies without any data on a comparison group were not considered eligible.

Outcomes: The outcomes of interest were the eligibility criteria for participation in the studies.

Study type: Only randomized controlled trials were considered for this review, including peer-reviewed studies reported written in the English language. Conference abstracts and non-peer-reviewed studies were not included. No eligibility criterion was applied on geography or journal were made.

Information Source and Literature Search Strategy

One trained author (Y.S.) searched the literature databases PubMed, Embase, the Cochrane Central, Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Preprint Citation Index, ProQuestTM Dissertations & Theses Citation Index, and SciELO Citation Index. The search was performed on 15 April 2024. No date restrictions were applied (i.e., searches included studies from the inception of the databases until the time of search which was 15 April 2024). Literature search details for each database is outlined in **Supplementary file 1**.

Study Selection, Data Items, Data Collection, and Synthesis

References extracted from the literature search were imported to EndNote X9.3.1. (Clarivate Analytics, Philadelphia, PA, USA). One author (E.T.S.B) removed duplicates and examined the titles and abstracts to remove obviously irrelevant records. Two authors (E.T.S.B. and A.A-V.) then independently examined the full text of the remaining references for eligibility and reviewed reference lists from these studies for any additional relevant studies. A third author (Y.S.) was invited to discuss disagreements and to reach a final consensus.

Data regarding study design, characteristics, methods, eligibility, and conclusion were extracted from eligible studies using extraction forms. Two authors (A.A-V. and R.EA) worked independently on the data extraction. A third author (Y.S.) was invited to discuss disagreements and to reach a final consensus.

All eligibility criteria across studies were summarized in text and tables. Eligibility criteria were summarized according to the categories: visual function, disease definition and stage, ocular co-morbidities, systemic co-morbidities, demographics, and miscellaneous.

Results

Study Selection

The literature search identified 4,920 records in total, where 2,245 of these were duplicates, and 2,610 were either not relevant for this review, or not written in the English language. Remaining 65 records were retrieved in full text for evaluation of eligibility. Reference list review identified one additional record. After careful review, 49 studies were deemed eligible for inclusion in the qualitative review (Fig. 1).

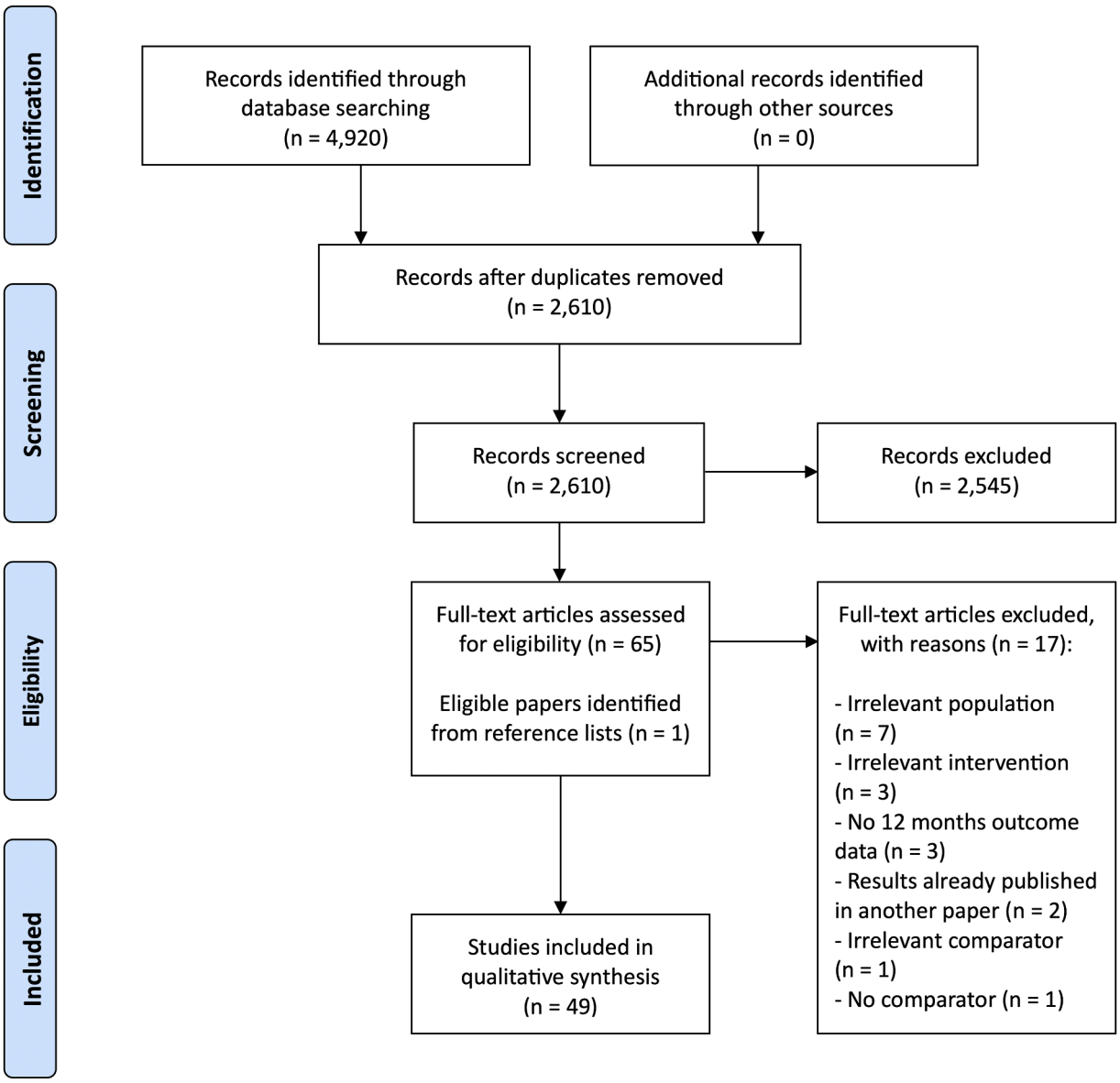

Fig. 1. PRISMA flow diagram of study selection.

Characteristics of Eligible Studies

Studies eligible for this systematic review summarized data from a total of 26,995 eyes of 26,995 patients. All studies included only one study eye per patient. The studies were designed as single-center (n = 12) or multi-center (n = 37) RCTs. The trials extended over various phases, where some were without defined phase classifications, as follows: Phase 1/2 (n=1), phase 2 (n=4), phase 3, (n=15), phase 3b (n=5), phase 3b/4 (n=1), phase 4 (n=6) and without phase (n=17). Details of the study arms and conclusion are summarized in detail in Table 1.

Eligibility criteria for visual function

All studies included a baseline criterion for visual function, specifically evaluating the best corrected visual acuity (BCVA). The minimum baseline values ranged from 18 to 50 ETDRS letters, and the maximum baseline values ranged from 69 to 78 ETDRS letters. An upper limit was not imposed in three studies[11–13]. A progression in nAMD, demonstrated by a decrease in BCVA, was required in three studies and defined as a loss of >1 Snellen line, >5 ETDRS letters, or >15 ETDRS letters within 6 months of baseline[14–16]. Eligibility criteria for the fellow non-study eye included a BCVA value of >20-34 ETDRS letters or >20/800-20/100[16–21]. Fellow non-study eye with BCVA of finger counting, hand motion, or worse was considered ineligible in four studies[22–25]. When both eyes were eligible, the study eye was selected based on the following criteria: 1) worse visual acuity[12,26], 2) best visual acuity[27], 3) potential for the best functional recovery[28], 4) the eye showing greater progression with loss of distance acuity[29], or 5) in agreement with the patient and study ophthalmologist[30]. A summary of all the BCVA criteria is provided in Table 2.

Eligibility criteria for disease definition and stage

The eligibility in all studies was defined by the presence of nAMD with an active classic or occult lesion, showing evidence of leakage on fluorescein angiography (FA), except one study which used optical coherence tomography (OCT)[52]. Three studies additionally required leakage on indocyanine green angiography (ICGA)[12,31,32]. OCT was used in 31 studies to document subretinal fluid (SRF), intraretinal fluid (IRF), or sub-retinal pigment epithelium (sub-RPE) fluid[12,13,17,18,22,25,28–44]. In

Table 1
Summary of studies in review.

Study name	Study type	N	Investigational arms	Conclusion
Amarakoon et al. 2019	Single-center, open-label, RCT	120	Bevacizumab • every 4 weeks • every 8 weeks	At 1 year, bevacizumab administration on-demand every 8 weeks was non-inferior to administration every 4 weeks.
Barikian et al. 2015	Single- center RCT, pilot study.	90	Bevacizumab • Biweekly Induction • Monthly Induction • Immediate As-Needed	When using the different treatment regimen with Bevacizumab, it seems that biweekly injections have a role to play in resistant cases but not in treatment-naive cases, where there seems to be no added benefit to monthly induction or immediate prn regimens.
Berg et al. 2015	Phase 4, Multicenter RCT	441	• Bevacizumab 1.25 mg • Ranibizumab 0.5 mg	Bevacizumab and Ranibizumab are equivalent at 1 year regarding the gain in visual acuity and reduction of CRT when using a treat-and-extend protocol. The visual acuity results are comparable to those with a monthly regimen.
Biswas et al. 2011	Single- center Prospective comparative case series	120	• Ranibizumab 0.5 mg • Bevacizumab 1.25 mg	Ranibizumab and bevacizumab are safe and efficacious treatment options as intravitreal injections in the treatment of CNVM due to AMD and that the two do not have statistically significant difference between them in terms of bringing about BCVA and CMT improvement.
Boyer et al. 2009	Phase 3b, Multicenter RCT	4300	Cohort 1: • Ranibizumab 0.3mg • Ranibizumab 0.5mg Cohort 2: • Ranibizumab 0.5mg	Intravitreal ranibizumab was safe and well tolerated in a large population of subjects with neovascular AMD. Ranibizumab had a beneficial effect on VA and retina anatomy.
Bressler et al. 2023	Phase 3, Multicenter RCT	705	• Ranibizumab biosimilar SB11 • Reference ranibizumab	Longer-term results of SB11 support its use, as a safe and effective RBZ biosimilar
Brown et al. 2006	Phase 3, Multicenter RCT	423	Monthly intravitreal injections: • Ranibizumab 0.3 mg plus sham verteporfin. • Ranibizumab 0.5 mg plus sham verteporfin • Sham injections plus active verteporfin therapy.	Ranibizumab was superior to verteporfin as intravitreal treatment of predominantly classic neovascular age-related macular degeneration, with low rates of serious ocular adverse events. Treatment improved visual acuity on average at 1 year.
Busbee et al. 2013	Phase 3, Multicenter RCT	1097	• Ranibizumab 0.5 mg monthly • Ranibizumab 0.5 mg PRN • Ranibizumab 2.0 mg monthly • Ranibizumab 2.0 mg PRN	The HARBOR results ultimately confirmed that the current, commercially available preparation of ranibizumab (0.5 mg), when dosed monthly, provides optimum results.
Chakravarthy et al. 2012	Multicenter, noninferiority factorial trial	628	• Ranibizumab • Bevacizumab • Continuous • Discontinuous	Ranibizumab and bevacizumab confer equivalent visual function benefits, but that bevacizumab is substantially less expensive. Ranibizumab, and continuous treatment, result in significantly better morphologic outcomes, but there was no similar difference in visual function.
Chan et al. 2015	Multicenter RCT	36	• Ranibizumab 0.5 mg monthly • Ranibizumab 0.5 mg PRN • Ranibizumab 2.0 mg monthly • Ranibizumab 2.0 mg PRN	Both 0.5 and 2.0 mg intravitreal ranibizumab induced similar overall visual and anatomic improvements at 12 months. Significantly, the improvements occurred much earlier for the 2.0 mg dose group.
Dugel et al. 2017	Phase 2, Multicenter RCT	90	• Brolucizumab 6 mg q12 • Aflibercept 2 mg q8	BCVA in brolucizumab-treated eyes appeared comparable to aflibercept-treated eyes, with more stable CSFT reductions, receipt of fewer unscheduled treatments, similar in safety and higher rates of fluid resolution.
Dugel et al. 2020	Phase 3, Multicenter, RCT	1817	HAWK • Brolucizumab 3 mg • Brolucizumab 6 mg • Aflibercept 2 mg HARRIER • Brolucizumab 6 mg • Aflibercept 2 mg	Brolucizumab was noninferior to aflibercept in visual function at Week 48, and >50% of brolucizumab 6 mg treated eyes were maintained on q12w dosing interval through Week 48. Anatomic outcomes favored brolucizumab over aflibercept. Overall safety with brolucizumab was similar to aflibercept
El-Mollayess et al. 2012	Multicenter, open-label, RCT	120	• Fixed interval dosing (every 4 to 6 weeks) with bevacizumab (1.25 mg/0.05 mL) • Variable dosing with intravitreal bevacizumab (1.25 mg/0.05 mL)	Fixed-interval and variable dosing regimens of intravitreal bevacizumab improved visual acuity and anatomic outcomes after 12 months in eyes with neovascular AMD. However, variable dosing had a reduced treatment burden.
Eldem et al. 2015	Multicenter, open-label, RCT	99	Ranibizumab 0.5 mg: • Wait & Extend • Treat & Observe	Using ranibizumab in a W&E regimen in patients with CNV secondary to AMD appeared to be as efficacious and well tolerated as a T&O regimen, with fewer clinic visits required.
Feltgen et al. 2017	Phase 4, single-center, RCT	40	• Ranibizumab 0.5 mg RABIMO group • Ranibizumab 0.5 mg PRN group	Results from the RABIMO trial demonstrate the non-inferiority of a fixed-bimonthly ranibizumab treatment regimen to the standard-of-care, that is, a PRN treatment scheme in eyes with nAMD—a regimen non-inferior in either functional or anatomical aspects or regarding safety.
Galvez et al. 2020	Phase 4, Multicenter, RCT	306	0.5 mg intravitreal ranibizumab in all 3 groups • Bimonthly • T&E regimen • PRN regimen	In anti-VEGF naıve patients with nAMD, this study confirms the noninferiority of fixed bimonthly and T&E regimens of intravitreal 0.5 mg ranibizumab to a PRN regimen at 12 months.
Gillies et al. 2019	Phase 4, Multicenter, RCT	281	• Ranibizumab 0.5 mg • Aflibercept 2.0 mg	The main finding from this preplanned interim analysis of the RIVAL study is that visual acuity gains at 12 months were not substantially different between ranibizumab and aflibercept for nAMD when using an identical TE regimen.

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Table 1 (*continued*)

Study name	Study type	N	Investigational arms	Conclusion
Gragoudas et al. 2004	Multicenter, RCT	1186	Pegaptanib • 0.3 mg • mg • mg • Sham	Treatment with pegaptanib provided a statistically significant and clinically meaningful benefit in a broad spectrum of patients with neovascular age-related macular degeneration, regardless of the size or angiographic subtype of the lesion or the baseline visual acuity.
Heier et al. 2012	Phase 3, Multicenter, RCT	2419	**VIEW 1** • Ranibizumab -0.5q4 • Intravitreal Aflibercept 2q4 • Intravitreal Aflibercept 0.5q4 • Intravitreal Aflibercept 2q8 **VIEW 2** • Ranibizumab -0.5q4 • Intravitreal Aflibercept 2q4 • Intravitreal Aflibercept 0.5q4 • Intravitreal Aflibercept 2q8	Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.
Heier et al. 2022	Phase 3, Multicenter, RCT	1329	TENAYA • Faricimab 6.0 mg up to every 16 weeks • Aflibercept 2.0 mg every 8 weeks • LUCERNE • Faricimab 6.0 mg up to every 16 weeks • Aflibercept 2.0 every 8 weeks	TENAYA and LUCERNE phase 3 trials evaluating dual Ang-2 and VEGF-A inhibition with intravitreal faricimab, administered at up to 16-week intervals, demonstrated vision benefits and anatomical outcomes comparable with VEGF pathway inhibition alone with aflibercept given at 8-week intervals.
Holz et al. 2022	Phase 3, Multicenter, RCT	477	• FYB201 • Reference Ranibizumab 0.5 mg	FYB201 is biosimilar to reference ranibizumab in terms of clinical efficacy and ocular and systemic safety in the treatment of patients with nAMD
Kertes et al. 2019	Phase 3, Multicenter, open-label, RCT	526	• Ranibizumab 0.5 mg • Treat and Extend • Monthly	T&E regimen was noninferior to a monthly dosing regimen. Similar visual outcomes in the T&E group as in the monthly dosing group were achieved with significantly fewer injections.
Khanani et al. 2020	Phase 2, Multicenter, RCT	76	• Ranibizumab, 0.5 mg, • Faricimab, 6.0 mg, every 12 weeks • Faricimab, 6.0 mg, every 16 weeks	Faricimab dosing every 16 weeks and every 12 weeks resulted in maintenance of initial vision and anatomic improvements comparable with monthly ranibizumab.
Krebs et al. 2013	Phase 3, Multicenter, RCT	321	• Ranibizumab 0.5 mg • Bevacizumab 1.25 mg	Bevacizumab was equivalent to ranibizumab for visual acuity at all time points over 1 year.
Kunimoto et al. 2020	Phase 3, Multicenter, RCT	1888	• Abicipar Q8 • Abicipar Q12 • Ranibizumab Q4	Abicipar Q8 and Q12 were both noninferior to ranibizumab Q4 in the primary end point of stable vision at week 52. Intraocular inflammation was more frequent with abicipar.
Lanzetta et al. 2024	Phase 3, Multicenter, RCT	1011	• Aflibercept 2 mg every 8 weeks • Aflibercept 8 mg every 12 weeks • Aflibercept 8 mg every 16 weeks	Aflibercept 8 mg administered at extended dosing intervals resulted in non-inferior visual gains and a superior and more durable drying effect than aflibercept 2 mg.
Li et al. 2014	Phase 2, Multicenter, RCT	122	Conbercept • 0.5-mg As Needed • 0.5-mgMonthly • 2.0-mg As Needed • 2.0-mg Monthly	The significant gains in BCVA at 3 months were the same or better at 12 months in all conbercept dosing groups of neovascular AMD patients.
Li et al. 2024	Phase 3, Multicenter, RCT	366	• QL1207 • Aflibercept	QL1207 has equivalent efficacy to aflibercept for nAMD with similar safety profiles.
Loewenstein et al. 2023	Phase 3, Multicenter, RCT	582	• XSB-001 • Ranibizumab 0.5 mg	XSB-001 demonstrated biosimilarity to reference ranibizumab in patients with nAMD. Treatment with XSB-001 for 52 weeks was generally safe and well tolerated, with a safety profile similar to the reference product.
Lushchyk et al. 2013	Single-center, open label, RCT	191	• Bevacizumab every 4 weeks • Bevacizumab every 6weeks • Bevacizumab every 8 weeks	At 1 year, bevacizumab administered every 6 or 8 weeks was not inferior to therapy administered every 4 weeks.
Mahmood et al. 2015	Single-center, RCT	331	Bevacizumab 1.25mg • PRN Arm • Routine Arm	The improvement in BCVA was broadly similar to that obtained in other studies using anti-vascular endothelial growth factor drugs with more frequent assessments and treatments.
Martin et al. 2011	Multicenter, RCT	1208	• Ranibizumab monthly • Bevacizumab monthly • Ranibizumab as needed • Bevacizumab as needed	At year 1, bevacizumab and ranibizumab had equivalent effect on visual acuity when administered according to the same schedule. Ranibuzumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibuzumab adminstrated monthly.
Menon et al. 2013	Single-center, open-label, RCT	100	Bevacizumab • Loading group • No loading Group	The results supported our hypothesis that a loading dose leads to slightly better visual stability in terms of proportions of patients experiencing moderate visual loss, but did not support the hypothesised difference in anatomical outcome.
Mishra et al. 2022	Single-center, RCT	120	• Brolucizumab 6 mg • Aflibercept 2mg	The results of the present study suggest non-inferiority of brolucizumab PRN regimen to aflibercept PRN regimen in treatment naïve nAMD. Indian patients while achieving longer inter-injection intervals.
Mitchell et al. 2021	Phase 3b/4, Multicenter, open-label, RCT	271	• Aflibercept 2 mg • Early-T&E • Late-T&E	Outcomes were similar between patients with neovascular age-related macular degeneration treated with an intravitreal aflibercept early-T&E or late-T&E regimen after initial dosing, with one injection difference over 2 years.
Nunes et al. 2019	Single-center, RCT	45	• Bevacizumab monthly • Bevacizumab biweekly • Ranibizumab monthly	The bi-weekly follow-up was effective and we found no significant differences in efficacy or safety between the treatments with ranibizumab and bevacizumab
Ohji et al. 2020	Phase 4, Multicenter, open-label, RCT	255	• Aflibercept 2 mg T&E with 2 weeks adjustment	Aflibercept administered to treatment-naivepatients with exudative AMD using two different T&E regimens, with a minimum injection interval of 8 weeks and a maximum interval of 16 weeks, improved and maintained

(*continued on next page*)

Table 1 (*continued*)

Study name	Study type	N	Investigational arms	Conclusion
			• Aflibercept 2 mg T&E with 4 weeks adjustment	functional and anatomic outcomes over 96 weeks, while minimizing the treatment burden on patients.
Regillo et al. 2008	Phase 3b, Multicenter, open-label, RCT	184	• Ranibizumab 0.3 mg • Ranibizumab 0.5 mg • Sham	Ranibizumab administered monthly for three months and then quarterly provided significant VA benefit to patients with AMD-related subfoveal CNV and was well tolerated.
Rosenfeld et al. 2006	Phase 3, Multicenter, RCT	716	• Ranibizumab0.3 mg • Ranibizumab0.5 mg • Sham	Intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization secondary to age-related macular degeneration.
Schauwvlieghe et al. 2016	Multicenter, RCT	327	• Bevacizumab 1.25 mg • Ranibizumab 0.5 mg	Bevacizumab was not inferior to ranibizumab. The response to bevacizumab was more var- ied with higher percentages of both gainers and losers and more frequently observed retinal fluid on SD-OCT at 12 months when compared to the ranibizumab group.
Schmidt-Erfurth et al. 2011	Phase 3b Multicenter, RCT	293	Ranibizumab • 0.3 mg quarterly • 0.5 mg quarterly • 0.3 mg monthly	After 3 initial monthly ranibizumab injections, both monthly (0.3 mg) and quarterly (0.3 mg/0.5 mg) ranibizumab treatments maintained BCVA in patients with CNV secondary to AMD. At month 12, BCVA gain in the monthly regimen was higher than that of the quarterly regimens.
Scholler et al. 2014	Single-center, RCT	55	• Ranibizumab • Bevacizumab	There was no difference in number of treatments, BCVA and CRT after 1 year between ranibizumab and bevacizumab in patients with nAMD.
Silva et al. 2018	Phase 3b Multicenter, RCT	650	• Ranibizumab 0.5 mg Treat and Extend • Ranibizumab 0.5 mg Monthly	Ranibizumab 0.5 mg administered according to a T&E regimen was statistically noninferior and clinically comparable with a monthly regimen in improving VA from baseline to the end of study. No new safety signals for ranibizumab were identified
Taipale et al. 2020	Single-center, open-label, RCT	52	• Aflibercept 2 mg • T&E moderate extentions • T&E rapid extentions	At one year, the anatomical and functional responses were comparable between the moderate and rapid extensions protocols, with fewer aflibercept injections in the rapid extension protocol.
Tano et al. 2010	Phase 1/2, Multicenter, open-label, RCT	88	Group 1 • Ranibizumab 0.3 mg • Ranibizumab 0.5 mg Group 2 • Ranibizumab 0.3 mg • Ranibizumab 0.5 mg	Ranibizumab was effective and well tolerated in Japanese patients with subfoveal CNV secondary to AMD.
Wang et al. 2019	Phase 4, Multicenter, open-label, RCT	108	• 1 dose + PRN (PRN group) • 3 loading doses + PRN (LD group)	One dose + PRN showed noninferior visual gains than 3 loading doses + PRN regimen using ranibizumab in Chinese nvAMD and PCV patients. Number of injections in the PRN group was similar as that in the LD group but remained a potential risk of vision instability during one-year follow-up using OCT-guided retreatment criteria
Woo et al. 2023	Phase 3, Multicenter, RCT	449	• SB15 • Aflibercept • Aflibercept/SB15 • Aflibercept/ Aflibercept	Efficacy, safety, PK and immunogenicity were comparable between SB15 and AFL and between switched and non-switched participants.
Wykoff et al. 2015	Phase 3b, Multicenter, RCT	60	• 0.5 mg ranibizumab • Monthly • Trex protokol	The TREX neovascular AMD management strategy used in this prospective, randomized, controlled trial resulted in visual and anatomic gains comparable with those obtained with monthly dosing.
Wykoff et al. 2023	Phase 2, Multicenteer, Open-label, RCT	106	• Aflibercept, 8mg • Aflibercept, 2mg	Although aflibercept, 8 mg, did not achieve the primary efficacy end point at week 16 at the 2-sided significance level of 5%, the observed trends in anatomic and visual improvements over 44 weeks with aflibercept, 8 mg, indicate potential additional therapeutic benefit over aflibercept, 2 mg. No new safety signals were observed over 44 weeks.

one study, OCT was used for only one of two cohorts: OCT findings determined the treatment regimen for cohort one, while BCVA loss guided treatment in cohort two[15].

The criteria for lesion size also varied across studies: 13 studies set a maximum lesion size of 12-disc areas (DA)[7,8,16,17,20,25,27,29,43,45–48], while four studies limited the size to ≤9.0 DA[22,23,39,49] and one study to ≤6 DA[23], all on FA, including blood, scars, and neovascularization. In 24 studies, the MNV component of the lesion had to cover at least 50% of the total lesion area[7,8,14,16–18,20–23,25,27,35,36,38–41,45–47,49–51], whilst lesions containing more than 50% blood or fibrosis were excluded in 22 studies[11,15–17,22,24,27,29,30,33–36,38–40,43–45,47,51,52]. Furthermore, two studies were considered eligible if there was evidence of lesion progression i.e., a >10% increase in CNV area based on FA[14,15]. A summary of these criteria is provided in Table 3.

Eligibility criteria for ocular co-morbidities

Previous photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis AG, Basel, Switzerland) was an exclusion criterion in 13 studies[11,19,22,23,26,29,38,44,46–49,54] and two studies excluded treatment within 30 days or 8-13 weeks from baseline[15,16]. PDT in the fellow non-study eye were considered ineligible if treatment had been received within 7-30 days of baseline in four studies[29,46–48]. Previous submacular surgery or other surgical intervention for nAMD was an exclusion criterion in 10 studies[7,8,14,15,18,27,30,36,47,55].

All studies excluded patients with MNV secondary to pathology other than nAMD (Table 4). MNV due to causes other than nAMD in the non-study eye was an exclusion criterion in nine studies[7,8,24,27,28,43,48,54,55].

Macular hole, RPE tear, and history of rhegmatogenous retinal detachment were exclusion criteria in 17, 18, and 10 studies, respectively[7,8,13,15,17,18,23–25,27,30,33,39,45,47,49,51].

Any sign of acute conjunctivitis, keratitis, scleritis, or endophthalmitis in the study eye would deem the eye ineligible in 16 studies[7,8,13,17,23–25,29,30,36,38,39,45,47,48,55]. A history of uveitis (infectious or non-infectious), scleritis, or intraocular inflammation following anti-VEGF in the non-study eye was an exclusion criterion in 18 studies[15–18,22,25,28–30,32,37–40,45,49,54,56].

Participants who had received any intravitreal corticosteroid injection, dexamethasone intravitreal implant in the study eye, or systemic corticosteroid treatment within 3-6 months of baseline, or any

Table 2
Eligibility criteria for visual function.

Study name	Criteria on visual function
Amarakoon et al. 2019	• BCVA of 20/200 to 20/20 assessed on ETDRS (Snellen equivalent).
Barikian et al. 2015	• BCVA of 50 letters or better on ETDRS. • (20/100 Snellen equivalent or better). • Eye with worse visual acuity enrolled if both eyes are eligible
Berg et al. 2015	• BCVA between 20/25 and 20/320.
Biswas et al. 2011	• BCVA between 35 and 70 ETDRS letters.
Boyer et al. 2009	• BCVA between 20/40 to 20/400 (Snellen equivalent). • Disease progression: loss of >5 ETDRS letters (or >1 Snellen line) within 6 months before study initiation.
Bressler et al. 2023	• BCVA of 20/40 to 20/200. • Letter score of 73 to 34 on ETDRS.
Brown et al. 2006	• BCVA of 20/320 to 20/40 assessed on ETDRS (Snellen equivalent).
Busbee et al. 2013	• BCVA of 20/40 to 20/320 (Snellen equivalent). • Documented visual loss of >1 line of Snellen vision.
Chakravarthy et al. 2012	• BCVA >25 letters on ETDRS.
Chan et al. 2015	• BCVA scores of >19 and <69 letters on ETDRS. • 20/400 to 20/40 (Snellen equivalent).
Dugel et al. 2017	• BCVA between 73 and 23 letters on ETDRS. • Participant's fellow eye must have had a BCVA of 20 letters (approximate Snellen equivalent 20/400) or better
Dugel et al. 2020	• BCVA between 78 and 23 letters at screening and baseline using ETDRS.
El-Mollayess et al. 2012	• BCVA, ETDRS charts, between 20/40 and 20/400 (Snellen equivalent).
Eldem et al. 2015	• BCVA score between 73 and 34 letters in the study eye. • Where both eyes were eligible, the eye with better VA was chosen for treatment unless the investigator deemed, based on medical justification, that the other eye was a more appropriate candidate for the study.
Feltgen et al. 2017	• BCVA in the study eye of 20/320 to 20/40 according to (ETDRS).
Galvez et al. 2020	• Baseline BCVA score between 23 and 78 letters using ETDRS chart at 4 m. • Approximately 20/25 and 20/320 (Snellen equivalent, respectively). • When both eyes were affected, the eye capable of best functional recovery according to the investigator's opinion was included.
Gillies et al. 2019	• BCVA letter score at both Screening and baseline must be 23 letters or more as measured by the 3 meters ETDRS-like charts. • Approximate Snellen equivalent to 3/60. • If both eyes are eligible at Screening and Baseline, the investigator will decide the study eye.
Gragoudas et al. 2004	• BCVA of 20/40 to 20/320 in the study eye • BCVA of 20/800 or better in the other eye. • Required loss of 15 or more letters (approximately 3 lines on the study eye chart) of visual acuity during the previous 12 weeks.
Heier et al. 2012	• BCVA of 73 to 25 letters on ETDRS chart. • 20/40 to 20/320 (Snellen equivalent).
Heier et al. 2022	• BCVA of 78–24 letters. • 20/32–20/320 (approximate Snellen equivalent). • Exclusion if BCVA of hand motion or worse in non-study eye.
Holz et al. 2022	• BCVA in the study eye, determined by standardized ETDRS testing, between 20/32 (0.63) and 20/100 (0.2) Snellen equivalent. • BCVA in the fellow eye, determined by standardized ETDRS testing, at least 20/100 (0.2) Snellen equivalent
Kertes et al. 2019	• BCVA score in the study eye between 19 and 78 letters using ETDRS charts at a testing distance of 4 m. • 20/32 - 20/400 at screening (Snellen equivalent).
Khanani et al. 2020	• BCVA letter score of 73 to 24 letters on ETDRS-like charts. • 20/40-20/320 (Snellen equivalent).
Krebs et al. 2013	• BCVA using ETDRS charts had to be 20/40 to 20/320. • If both eyes were eligible for inclusion in the present study, the eye that showed more. progression (loss of distance acuity) based on the local investigator's assessment was included.
Kunimoto et al. 2020	• BCVA of ≤73 and ≥24 ETDRS letters. • 20/40 to 20/320 (Snellen equivalent) at screening and baseline. • Non-study needed a BCVA of 34 ETDRS letters or better (20/200 Snellen equivalent)
Lanzetta et al. 2024	• BCVA on ETDRS letter score of 78 to 24 • Approximately 20/32 to 20/320 (Snellen equivalent) • Only one functional eye, even if that eye was otherwise eligible for the study (e.g., BCVA of counting fingers or less in the eye with worse vision).
Li et al. 2014	• BCVA letter scores in the study eye between 73 and 24 on ETDRS chart.
Li et al. 2024	• BCVA letter score of 73–34 using ETDRS.
Loewenstein et al. 2023	• BCVA was < 73 and > 49 ETDRS letters. • 20/40 to 20/100 (Snellen equivalent).
Lushchyk et al. 2013	• BCVA of 20/200 to 20/20 (Snellen equivalent) using ETDRS charts.
Mahmood et al. 2015	• BCVA letter score must be between logMAR 0.3 – 1.2 • 6/12 to 6/96 (Snellen equivalent).
Martin et al. 2011	• BCVA in the study eye, using e-ETDRS testing, between 20/40 and 20/320 (Snellen equivalent). • Only one eye will be assessed in the Lucentis-Avastin Trial study. • If both eyes are eligible, the patient and study ophthalmologist will select the eye for entry.
Menon et al. 2013	• Best Corrected Visual Acuity (BCVA) 20/40 - 20/320 • BCVA in no study eye better than 20/320
Mishra et al. 2022	• Best-corrected visual acuity between 20/32 to 20/400
Mitchell et al. 2021	• BCVA using ETDRS of 73–25 letters • Approximately 20/40–20/320 (Snellen equivalent)
Nunes et al. 2019	• BCVA ETDRS letter score between 20 and 80 • 20/25 and 20/400 (Snellen equivalent)
Ohji et al. 2020	• BCVA of 73–25 using ETDRS letters • Approximately 20/40–20/320 (Snellen equivalent) in the study eye.If both eyes met the inclusion criteria, the eye with the worst BCVA was selected as the study eye
Regillo et al. 2008	BCVA, using ETDRS charts, of 20/40 to 20/320 (Snellen equivalent).
Rosenfeld et al. 2006	• BCVA, using ETDRS charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye.
Schauwvlieghe et al. 2016	• BCVA score between 78 and 20 letters • Approximately 0,63–0,05 (Snellen equivalent).
Schmidt-Erfurth et al. 2011	• BCVA score between 73 and 24 letters • Approximately 20/40 to 20/320 (Snellen equivalent). • BCVA score of <34 letters in both eyes resulted in exclusion.
Scholler et al. 2014	• BCVA between 20/40 and 20/320
Silva et al. 2018	• BCVA score must be ≤78 and ≥23 letters at 4 meters starting distance using ETDRS (approximate Snellen equivalent of 20/32 and 20/320)
Taipale et al. 2020	• BCVA was 20–75 ETDRS letters.
Tano et al. 2010	• BCVA score between 73 and 24 letters in the study eye approximate Snellen equivalent of 20/40 to 20/320), assessed with ETDRS charts. • Patients were excluded if they had a BCVA score of <34 letters in both eyes
Wang et al. 2019	• BCVA scores both should be between 78 and 23 words. • Approximately equals to 20/30-20/320 (Snellen vision chart units).
Woo et al. 2023	• BCVA of 20/40 to 20/200 (letter score of 73 to 34, inclusive) using ETDRS at screening and at Week 0 (Day 1) prior to randomization • Subject with only one functional eye (defined as BCVA of counting finger or less on the eye
Wykoff et al. 2015	• BCVA using ETDRS with between 78 and 18 (Snellen equivalent, 20/32 to 20/500)
Wykoff et al. 2023	• BCVA using ETDRS letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320). • Only 1 functional eye, even if that eye was otherwise eligible for the study (eg, BCVA of counting fingers or less in the eye with worse vision).

Table 3
Eligibility criteria for disease definition and stage.

Study name	Criteria on neovascular AMD (definition/lesion/diagnosis)
Amarakoon et al. 2019	• Neovascular AMD with leakage on FA and ICGA. • OCT with presence of SRF or sub-RPE fluid.
Barikian et al. 2015	• Neovascular AMD with SRF or sub-RPE fluid, leakage on FA and ICGA. • Additionally, presence of subretinal fluid, cystic maculopathy, or central retinal thickness>250mm had to be documented on optical coherence tomography (OCT). • CNV less than 5400 mm in greatest linear dimension.
Berg et al. 2015	• Neovascular AMD with IRF or SRF, leakage on FA. • Lesions must have <50 % fibrosis or blood. Intraretinal or subretinal fluid as determined by optical coherence tomography (OCT).
Biswas *et al.* 2011	• Neovascular AMD with active classic or occult lesion on FA.
Boyer *et al.* 2009	• Neovascular AMD with classic or occult CNV on FA with evidence of recent disease progression. • Lesions must have <50 % fibrosis or blood.
Bressler *et al.* 2023	• Neovascular AMD with SRF or IRF, leakage on FA. • CNV area ≥ 50% of the total lesion area • A total lesion area of ≤9.0 disc areas (DA) in size (including blood, scars and neovascularization)
Busbee *et al.* 2013	• Neovascular AMD with active classic or occult CNV on FA. • Evidence of recent disease progression. • CNV area ≥ 50% of the total lesion area on FA.
Brown *et al.* 2006	• Neovascular AMD with active predominantly classic subfoveal CNV area ≥ 50% of the total lesion area on FA. • Total area of lesion < 12 disc area or 30.48 mm^2
Chakravarthy *et al.* 2012	• Neovascular AMD with activity on FA • Lesions must have <50 % fibrosis or blood.
Chan *et al.* 2015	• Neovascular AMD with activity on FA and OCT. • Lesions must have <50 % fibrosis or blood. • Total area of lesion < 12 disc area
Dugel *et al.* 2017	• Neovascular AMD with leakage on FA. • OCT with SRF, IRF, or sub-RPE fluid. • CNV area ≥ 50% of the total lesion area on FA. • Lesions must have <50 % fibrosis or blood.
Dugel et al. 2020	• Neovascular AMD with classic or occult CNV on FA. • CNV area ≥ 50% of the total lesion area on FA. • OCT with SRF or IRF. • Lesions must have <50 % fibrosis or blood.
El-Mollayess et al. 2012	• Neovascular AMD with subfoveal CNV on FA. • OCT with SRF or IRF and CNV less than 5400 micrometers in greatest linear dimension.
Eldem et al. 2015	• Neovascular AMD with classic or occult CNV on FA. • CNV area ≥ 50% of the total lesion area on FA. • Lesions must have <50 % fibrosis or blood. • Total lesion area ≤ 12 disc areas for minimal classic/ occult lesions • ≤ 9 disc areas for the classic lesions.
Feltgen et al. 2017	• Neovascular AMD on FA and OCT. • CNV size ≤ 50% of the PED • Membrane size: ≤12 disc diameters (DD) • Lesions must have <50 % fibrosis or blood.
Galvez et al. 2020	• Neovascular AMD with evidence of CNV lesion activity based on hemorrhages. • Leakage from CNV on FA. • OCT with IRF or SRF.
Gillies et al. 2019	• Neovascular AMD with leakage on FA. • OCT with IRF SRF, or sub-RPE fluid.
Gragoudas et al. 2004	• Neovascular AMD with active classic or occult CNV on FA. • CNV size ≤ 50% of the PED, Lesions must have <50 % fibrosis or blood. • lesion sizes up to and including 12-disc areas (including blood, scar/atrophy, and neovascularization) were permitted.
Heier et al. 2012	• Neovascular AMD with CNV of any subtype. • CNV area ≥ 50% of the total lesion area on FA. • Lesions must have <50 % fibrosis or blood.
Heier et al. 2022	• Neovascular AMD with exudation on OCT. • CNV area ≥ 50% of the total lesion area on FA. • Lesions must have <50 % fibrosis or blood
Holz et al. 2022	• A total lesion size (including blood, atrophy, fibrosis, and neovascularisation) of ≤9 disc areas on FFA • Neovascular AMD with fovea-involving IRF or SRF on OCT. • CNV area ≥ 50% of the total lesion area on FA. • lesions must have <50 % fibrosis or blood. • Total area of whole lesion had to be equal or less than 12-disc areas.
Kertes et al. 2019	• Neovascular AMD was assessed with leakage on FA.
Khanani et al. 2020	• Neovascular AMD with activity on FA with CNV area ≥ 50% of the total lesion area. • Total lesion size (including blood, atrophy, fibrosis, and neovascularization) of 6 disc areas or less by FA OCT with presence of fluid. • <50 % fibrosis or blood.
Krebs et al. 2013	• Neovascular AMD with leakage on FA, OCT with presence of IRF or SRF. <50 % fibrosis or atrophy. • The total lesion area must be 12 disc areas or less in size.
Kunimoto et al. 2020	• Neovascular AMD with leakage on FA, OCT with presence of IRF or SRF.. • CNV area ≥ 50% of the total lesion area, <50 % fibrosis or blood.
Lanzetta et al. 2024	• Neovascular AMD activity on FA. • CNV area ≥ 50% of the total lesion area, OCT with presence of IRF or SRF affecting the center subfield. • Total lesion size >12 disc areas (30.5 mm2, including blood, scars, and neovascularisation) as assessed by fluorescein angiography in the study eye.
Li et al. 2014	• Neovascular AMD with leakage on FA, OCT with presence of IRF or SRF • Lesions must have <50 % fibrosis or blood.
Li et al. 2024	• Neovascular AMD with leakage on FA, OCT with presence of IRF or SRF • CNV comprising ≥ 50% of the total lesion area. • Total lesion area (including areas of CNV, blood, and scar) < 12-disc areas.
Loewenstein et al. 2023	• Neovascular AMD with leakage on FA, CNV area ≥ 50% of the total lesion area. • OCT with presence of IRF or SRF. • The total lesion area was < 9.0-disc areas in size, including blood, scars, and neovascularization. • Lesions must have <50 % fibrosis or blood.
Lushchyk et al. 2013	• Neovascular AMD with leakage on FA and ICGA. • OCT with presence of SRF or sub-RPE fluid.
Mahmood et al. 2015	• Neovascular AMD with any classic CNV or progressing minimally classic or occult CNV on FA and OCT. • CNV area ≥ 50% of the total lesion area, ≤ 50% of fibrosis or hemorrhage.
Martin et al. 2011	• Neovascular AMD with leakage on FA. • OCT with SRF or sub-RPE fluid. • CNV size ≤ 50% of the PED. • Lesions must have <50 % fibrosis or blood.
Menon et al. 2013	• Neovascular AMD with minimally classic or occult CNV on FA.
Mishra et al. 2022	• Neovascular AMD with active CNV on FA. • CNV area ≥ 50% of the total lesion area. • OCT with IRF and SRF.
Mitchell et al. 2021	• Neovascular AMD with active CNV on FA. • CNV area ≥ 50% of the total lesion area.
Nunes et al. 2019	• Neovascular AMD with leakage on FA, OCT with presence of IRF or SRF
Ohji et al. 2020	• Neovascular AMD with active CNV on FA.
Regillo et al. 2008	• Neovascular AMD with any classic CNV or progressing minimally classic or occult CNV on FA. • CNV area ≥ 50% of the total lesion area. • The total lesion area must be 12 disk areas or less in size. • ≤ 50% of fibrosis or hemorrhage.
Rosenfeld et al. 2006	• Neovascular AMD with minimally classic or occult CNV, CNV area ≥ 50% of the total lesion area on FA • The total lesion area must be 12-disc areas or less in size ≤ 50% of fibrosis or hemorrhage.
Schauwvlieghe et al. 2016	• Neovascular AMD with activity on FA and OCT. • Subretinal fibrosis or haemorrhage if the size of the haemorrhage is > 70% of the lesion. • The total lesion area should be < 12 disc areas.

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Table 3 (*continued*)

Study name	Criteria on neovascular AMD (definition/lesion/diagnosis)
Schmidt-Erfurth et al. 2011	• Neovascular AMD with an active classic or occult CNV on FA. • CNV area ≥ 50% of the total lesion area. • The total lesion area ≤12 disc areas for minimally classic or occult with no classic component. • ≤9 disc areas (5400 μm) for predominately classic lesions.
Scholler et al. 2014	• Neovascular AMD with FA verified activity. • The total lesion area must be 12 disc areas or less in size.
Silva et al. 2018	• Neovascular AMD with active leakage on FA, • OCT with IRF and SRF. • Total area of fibrosis < 50% of the lesion area.
Taipale et al. 2020	• Neovascular AMD on OCT and FA.
Tano et al. 2010	• Neovascular AMD with classic or occult CNV on FA, CNV area ≥ 50% of the total lesion area.
Wang et al. 2019	• Neovascular AMD on OCT and FA. • ICGA was performed when PCV was suspected.
Woo et al. 2023	• Neovascular AMD on OCT and FA with CNV area ≥ 50% of the total lesion area. • Total lesion area ≤ 9.0 Disc Areas (DA) in size (including blood, scars, and eovascularization)
Wykoff et al. 2015	• Neovascular AMD on OCT. • Area of subretinal hemorrhage and fibrosis < 50 % of the total lesion.
Wykoff et al. 2023	• Neovascular AMD on FA, OCT with IRF and SRF. • Area of subretinal hemorrhage and fibrosis < 50 %.

corticosteroid treatment at all were exclusion criteria in 17 studies[12,16–18,22,25,28,30,35,36,38–40,49,56].

Patients with planned or any history of intraocular surgery in the study eye were excluded in 32 studies[7,8,13–19,22–27,29,30,32,35,38–40,42,45–49,51,53–55].

Diabetic retinopathy of any stage would deem the eye ineligible in 29 studies[1,7,8,11–18,22–25,28–30,33,37–39,41,45,47–49,51,53], although mild diabetic retinopathy was acceptable in 3 of these studies[17,23,49]. Neovascularization of the iris at screening and previous panretinal photocoagulation were exclusion criteria in respectively 5 studies[13,18,24,28,55] and 22 studies[7,8,16–18,20–22,25,27,30,33,38,39,43,45–47,49,54–56]. In two studies, panretinal photocoagulation within one month of baseline would deem the patients ineligible for enrollment[29,48].

Intraocular pressure >25 mmHg prior to mydriasis or uncontrolled glaucoma (30 mmHg or higher) would deem the eye ineligible in 21 studies[7,8,13,15,17,19,24–26,28–30,33,36,44–47,49,50]. Concurrent use of prostaglandin-containing eye drops, or the use of more than one IOP lowering agent were exclusion criteria in nine studies[12,16–18,25,36,38,39,54].

Impaired visualization of the retina due to vitreous hemorrhage, corneal dystrophy or other media opacity that hindered high-quality retinal imaging were exclusion criteria in eight studies[23,25,33,37,39,42,51,52].

Myopia exceeding 6-8 diopters, axial length of ≥26 mm, a history of irregular astigmatism or amblyopia, along with a "chronic limitation of BCVA" in the study eye was deemed ineligible in 20 studies[7,8,11,15–18,22,23,25,29,30,33,38,39,43,45,47,51,53]. The absence of a non-study eye was an exclusion criterion in one study[22].

Additionally, the use of medications known to be toxic to the lens, retina, or optic nerve—such as deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines, and ethambutol—deemed patients ineligible in five studies[17,23,44,49,55]. Treatments such as transpupillary thermotherapy and radiation therapy were reason for excluded in 14 studies[8,14,17,20–22,27,38,46,47,49,54–56]. All criteria on ocular comorbidities are summarized in Table 4.

Criteria on systemic co-morbidities

History or evidence of severe cardiac disease (New York Heart Association functional class III or IV), ongoing treatment or a diagnosis of an unstable angina was considered an exclusion criterion in four studies[11,16,40,56]. In eight studies, patients with cardiovascular events that had occurred within less than 3-6 months before screening were excluded[12,22,24,25,31,32,46,54]. Any history of cardiovascular, cerebrovascular, and peripheral vascular events was considered a reason for ineligibility in seven studies[11,12,15,24,30,53,54]. Patients with hypertension with a blood pressure of >180/100 mmHg, 160/95-100 mmHg, >140/90 mmHg or with the definition of 'hypertension' were excluded respectively in five, six, one study and four studies, respectively[22–24,38,46].

History of certain diseases was a reason for ineligibility. For example, three studies excluded patients with uncontrolled diabetes mellitus[23,24,54]. Other examples of exclusion criteria include patients with a metabolic dysfunction, that were present in 13 studies[7,8,14,15,22,24,25,30,36,38,47,49,51], patients with renal failure that required dialysis in three studies[24,25,54], immunocompromised patients in two studies[23,31], or a history of recurrent significant or bacterial infections in two studies[15,30].

Participants with known allergic reactions or hypersensitivity to anti-VEGF, any investigational product ingredients, fluorescein sodium, or ICG dye were excluded in 22 studies[7,14,18,19,23–26,29–32,40,42,43,45–49,51,54]. Pregnant or lactating women were deemed ineligible in 16 studies[11,13,18,23–26,35,36,38,40,44–46,49,51]. All criteria on systemic comorbidities are summarized in Table 4.

The most frequent exclusion criteria across studies were any history of following: intraocular surgery (including cataract surgery), diabetic retinopathy, panretinal photocoagulation, glaucoma, and myopia. The number of studies with exclusion criteria related to ocular comorbidities are summarized in Fig. 2.

Eligibility criteria for demographics

A few criteria concerning age and sex demographics were observed. In most studies, an inclusion criterion of both female and male sexes, as well as a minimum age of 50 years was seen. One study had an inclusion criterion of age ≥ 60 years[43], while another study specified an age range of 60-90 years[57]. Two other studies required an inclusion criterion specifying that patients needed to be 65 years or older[31,32]. All criteria on demographics are provided in **Supplementary file 2**.

Miscellaneous eligibility criteria

In 34 studies, a common criterion was ensuring procedural patient compliance, as well as the provision of written informed consent[7,8,12,13,15,17–19,22–25,28–30,32–39,43–51,55,56].

A further 23 studies had exclusion criteria regarding reproductive factors: for males with female partners or for females of childbearing potential, and the use of contraception was stated as a requirement for eligibility[7,8,13–15,17,18,22–25,30,33–36,38–40,44,46,47,49,54]. Participation in other clinical trials for both systemic and intravitreal anti-VEGF treatment—both prior to and within 1-3 months to baseline—deemed patients ineligible in 21 studies[7,8,14,15,18–20,22–27,29,33,35,38,47–49,51]. All the miscellaneous criteria are summarized in **Supplementary file 3**.

Discussion

This systematic review identified an extensive list of eligibility criteria from the 49 RCTs that were analyzed, including factors such as demographics, visual acuity, disease definition and staging, ocular as well as systemic co-morbidities, and miscellaneous factors. Eligibility criteria are a crucial component of the clinical trials as they define the study population[58]. Clinical trials often aim to select populations that align with theoretical medicine, prioritizing patients who are most likely to benefit from treatment, rather than those who needed it the most[59,60]. In real-world clinical practice, patients present with a larger

Table 4
Eligibility criteria for co-morbidities.

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
Amarakoon et al. 2019	**Study eye** • If any other significant ocular disorders affecting visual acuity were present. • Patients had an ocular surgery planned during the 1-year follow-up period.	• Allergy to either FA or ICG dye injections was known. • Patients who used coumarin derivatives at the time of inclusion. • Patients who experienced clinically significant cerebrovascular accident or myocardial infarction in the 6 months prior to planned inclusion. • Patients who were immunocompromised.
Barikian et al. 2015	**Study eye** • Prior treatment for CNV • All CNV lesion types included except retinal angiomatous proliferation and polypoidal choroidal vasculopathy Corneal, lenticular, or vitreous opacification affecting quality of angiograms or OCT • History of vitrectomy, proliferative diabetic retinopathy, or other ocular conditions affecting vision **Either eye** • History of uveitis.	• Cardiovascular, cerebrovascular, and peripheral vascular events less than 6 months prior to enrollment
Berg et al. 2015	**Study eye**Previous treatment of CNV.CNV of other pathogenesis, such as pathologic myopia (defined as having a spherical equivalent of >8 diopters myopia) or Presumed Ocular Histoplasmosis Syndrome (POHS).Presence of retinal diseases other than AMD (diabetic retinopathy, macular hole, etc) that lead to loss of visual acuity.Impaired visualization of the retina (by vitreous hemorrhage, corneal dystrophy, etc.) that may hamper adequate diagnosis. Intraocular pressure ≥25 mm Hg, measured before mydriasis, or uncontrolled glaucoma as evaluated by the examining ophthalmologist. Active uveitis.Cataract that will presumably require operation within 2 years or other intraocular surgery or laser treatment during the last 3 months. **Either eye** • Infection in one or both eyes. **Non-study eye** • Anti-VEGF treatment during the last 4 weeks. • Intraocular inflammation after use of Lucentis or Avastin. **Other** • Earlier or current treatment with systemic anti-VEGF drug	Serious disease where there is a probability of death within the duration of the study.
Biswas et al. 2011	**Study eye** • Coexisting ocular pathology (advanced cataract, high myopia, chorio-retinal atrophic patches, diabetic retinopathy, glaucoma) • History of ocular surgery within the last 6 months **Either eye** • Previous treatment for CNV. **Other** • One-eyed patient	• History of cerebrovascular accident and myocardial infarction.
Boyer et al. 2009	**Study eye** • Previous submacular surgery or surgical intervention for AMD. • Verteporfin photodynamic therapy, pegaptanib sodium, or other AMD therapy within 30 days before day 0 • A tear in the retinal pigment epithelium involving the macula. • Any current intraocular condition (e.g., cataract or diabetic retinopathy) that, in the investigating physician's opinion, would require medical or surgical intervention during the 12-month study period or, if allowed to progress untreated, would likely contribute to the loss of at least 2 Snellen equivalent lines of VA over the 12-month study period. • Active intraocular inflammation (grade trace or above). • Current vitreous hemorrhage in the study eye • History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4). • Aphakia or pseudophakia with absence of the posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) • Spherical equivalent of the refractive error demonstrating more than -8 diopters of myopia • Intraocular surgery (including cataract surgery) within 2 months preceding Day 0 • Uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication) • Concurrent use of more than one therapy for glaucoma • History of glaucoma filtering surgery. • History of corneal transplant.	Pregnancy or lactation. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. Current treatment for a significant active systemic infection. Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders. History of recurrent significant infections or bacterial infections.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	Either eye • CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia • Intravitreal administration of bevacizumab within 30 days before day 0 • History of idiopathic or autoimmune-associated uveitis. • Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis. **Other** • Current use of systemic anti-VEGF agents	
Bressler et al. 2023	**Study eye** • Prior treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment laser photocoagulation) and which were not allowed during the study period. • Retinal pigment epithelial tears or rips involving the macula. • Presence of macular hole at any stage • Concurrent macular abnormality other than AMD affecting IP efficacy. • Any ITV injection of corticosteroid (e.g., triamcinolone acetonide) or ITV corticosteroid implant within 180 days prior to randomization, and which was not allowed during the study period. • History of vitrectomy, trabeculectomy, or other surgical interventions. • Any other intraocular surgery (including cataract surgery) or periocular surgery within 90 days prior to randomization, except for lid surgery, which may not have taken place within 30 days prior to randomization. • Spherical equivalent of the refractive error demonstrated more than 8 diopters of myopia. For subjects who underwent previous refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye was not to exceed 8 diopters of myopia. • History of retinal detachment. • History of full-thickness macular hole. • History of corneal transplantation surgery. • Presence of advanced glaucoma or optic neuropathy that affected or threatened the central visual field. • Uncontrolled ocular hypertension (defined as intraocular pressure $\geq$ 25 mmHg despite treatment with anti-glaucoma medication). • Prior treatment with pan-retinal photocoagulation and which were not allowed during the study period. **Either eye** • Any previous ITV anti-vascular endothelial growth factor (anti-VEGF) treatment (e.g., bevacizumab, aflibercept, ranibizumab) to treat neovascular AMD. • CNV due to other causes (e.g., ocular histoplasmosis, trauma) • History or clinical evidence of diabetic retinopathy (except for mild nonproliferative diabetic retinopathy) or diabetic macular edema. • History of idiopathic or autoimmune uveitis. **Other** • Current use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin and ethambutol, and which were not allowed during the study period.	• Stroke, transient ischemic attacks, or myocardial infarction within 90 days prior. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicated the use of an IP in the opinion of the investigator. • Pregnant or lactating women. A serum pregnancy test was required for women of childbearing potential at screening. • History of recurrent significant infections and/or current treatment for active systemic infection. • Known allergic reactions and/or hypersensitivity to ranibizumab or to any ingredients of the IP. • History of allergy to the fluorescein sodium for injection.
Brown et al. 2006	**Study eye** • Prior treatment with verteporfin, external-beam radiation therapy, or transpupillary thermotherapy (TTT). • Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation). • History of submacular surgery or other surgical intervention for AMD. • Previous subfoveal focal laser photocoagulation. • Laser photocoagulation (juxtafoveal or extrafoveal) within 1-month preceding Day 0. • History of vitrectomy surgery. • Retinal pigment epithelial tear involving the macula. • Any concurrent intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the Investigator could either: (1) Require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition, or (2) If allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 24-month study period • Active intraocular inflammation (grade trace or above). • Current vitreous hemorrhage.	• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. • Current treatment for active systemic infection.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4). • Aphakia or absence of the posterior capsule. • Spherical equivalent of the refractive error demonstrating more than -8 diopters of myopia. • Intraocular surgery (including cataract surgery) within 2 months preceding Day 0 • Uncontrolled glaucoma in the (defined as intraocular pressure ≥30 mmHg despite treatment with anti-glaucoma medication) • History of glaucoma filtering surgery. • History of corneal transplant. **Either eye** • CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia • History of idiopathic or autoimmune-associated uveitis. • Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis. **Non-study eye** • Treatment with verteporfin in less than 7 days preceding Day 0.	
Busbee et al. 2013	**Study eye** Previous intravitreal drug delivery (eg, intravitreal corticosteroid injection, anti-angiogenic drugs, or device implantation). Prior treatment with Visudyne(R), external-beam radiation therapy, or transpupillary thermotherapy (TTT). History of vitrectomy surgery, submacular surgery, or other surgical intervention for age-related macular degeneration (AMD). Retinal pigment epithelial tear involving the macula. Any concurrent intraocular condition in the (eg, cataract or diabetic retinopathy) that, in the opinion of the investigator, could either: Require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition; or if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity (BCVA) over the 24-month study period **Non-study eye** Treatment with Visudyne(R) in < 7 days preceding Day 0. **Either eye** CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.	• Uncontrolled blood pressure. • Atrial fibrillation not managed by patient's primary care physician or cardiologist within 3 months of screening visit. • History of stroke within the last 3 months of screening visit. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications. • Current treatment for active systemic infection. • Active malignancy. • History of allergy to fluorescein, not amenable to treatment.
Chakravarthy et al. 2012	**Study eye** • Presence of other active ocular disease causing concurrent vision loss, e.g. diabetic retinopathy • Previous treatment with PhotoDynamic Therapy (PDT) or a VEGF inhibitor. • Patients with 8 or more dioptres of myopia.	Pregnant and or lactating women. Past medical history of cardiovascular disease or cardiovascular comorbidity, e.g. Previous myocardial infarction or stroke, current angina, will not be an exclusion criterion. However, such factors will be documented carefully at the time of recruitment, and the potential benefits and harms of treatment discussed carefully with potential participants.
Chan et al. 2015	**Study eye** • Anti-VEGF therapy within the past 30 days • More than one prior PDT session. • Treatment of AMD in past 30 days. • Any cause of CNV and PED other than AMD. • Serous PED without CNV; PED with polypoidal choroidal vasculopathy (PCV).	• Not mentioned • Presence of any advanced systemic condition or end stage disease. • Advanced Alzheimer syndrome. • End stage cancer, etc., which will likely prevent patient from completing study.
Dugel et al. 2017	**Study eye** • Any approved or investigational treatment for exudative AMD other than vitamin supplements. • Any current or history of macular or retinal disease other than exudative AMD. Any concurrent intraocular condition that, in the opinion of the Investigator, could require medical or surgical intervention during the course of the study to prevent or treat vision loss, or that limits the potential to gain visual acuity with the investigational product.Uncontrolled glaucoma.Any ocular disease that, in the opinion of the Investigator, could compromise the visual acuity. History of eye surgery, as specified in protocol.Use of corticosteroids, as specified in protocol**Either eye**Any active ocular or periocular infection or active intraocular inflammation.	Any medical condition that, in the opinion of the Investigator, would preclude scheduled study visits, completion of the study or safe administration of investigational product. Any screening laboratory result that, in the opinion of the Investigator, would make the patient unsuitable for study participation. History of hypersensitivity to any component used in the study, as assessed by the Investigator.
Dugel et al. 2020	**Study eye** • Previous submacular surgery, other surgical intervention or laser treatment for AMD • Retinal pigment epithelium rip/tear in the study eye at screening or baseline	• History of a medical condition (disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding) that, in the judgement of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product. • History of hypersensitivity to any component of the test article, control article, or clinically relevant sensitivity to fluorescein dye (or indocyanine green for patients in Japan [HAWK]), as assessed by the Investigator.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• Current vitreous hemorrhage or history of vitreous hemorrhage within 4 weeks prior to baseline • Any history or evidence of a concurrent intraocular condition in the, including retinal diseases other than neovascular AMD, that, in the judgment of the Investigator, could require either medical or surgical intervention during the course of the study to preventor treat visual loss that might result from that condition or that limits the potential to gain visual acuity upon treatment with the investigational product. • Previous therapeutic radiation near the region. • History or evidence of the following. • Intraocular or refractive surgery within the 90-day period prior to baseline. • Previous penetrating keratoplasty or vitrectomy. • Previous panretinal. photocoagulation • Uncontrolled glaucoma defined as intraocular pressure greater than 25 mm Hg on medication or according to Investigator's judgment at screening or baseline. • Aphakia and/or absence of the posterior capsule at screening or baseline • Intra- or periocular use of corticosteroids during the 6-month period prior to baseline. • Use of topical ocular corticosteroids for 60 or more consecutive days within the 90-day period prior to baseline. **Either eye** • Any active intraocular or periocular infection or active intraocular inflammation (eg, infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) at baseline **Non-study eye** • Treatment with aflibercept (EYLEA®), bevacizumab (AVASTIN®), or pegaptanib (MACUGEN®) within the 4-week period prior to baseline • Ranibizumab (LUCENTIS®) within the 2-week period prior to baseline. **Other** • Use of systemic corticosteroids for 30 or more consecutive days within the 90 days prior to baseline, with the exception of low stable doses of corticosteroids (defined as 10 mg or lower prednisolone or equivalent dose used for 90 days or more prior to baseline). Inhaled, nasal, or dermal steroids are permitted.	• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a woman after conception and until termination of gestation, confirmed by a positive human chorionic gonadotropin pregnancy test, and women of childbearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at baseline, unless they are using effective methods of contraception during dosing of study treatment.
El-Mollayess et al. 2012	**Study eye** • Media opacity that would prevent good quality retinal imaging. • History of uveitis, vitrectomy, diabetic retinopathy, or other condition that may affect vision.	• Thromboembolic event less than 6 months prior to enrollment.
Eldem et al. 2015	**Study eye** • Previous treatment for AMD in the except juxtafoveal or extrafoveal laser photocoagulation administered at least 1 month before the study. • Previous or current intravitreal or sub-Tenon's agent. • Previous submacular surgery or any other surgical intervention. • Vitreous haemorrhage or rhegmatogenous retinal detachment or macular hole in the. • Any ocular condition that may require medical or surgical management for treatment or which, if left untreated, may result in loss of at least two lines of BCVA. • A tear in the retinal pigment epithelium of the study eye involving the macula. • Previous treatment with verteporfin, external beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy or transpupillary thermotherapy before the study **Either eye** • Patients with CNV in either eye due to other causes.	
Feltgen et al. 2017	**Study eye** • Previous injection of anti-angiogenic substances • Pigment epithelial detachment without detectable membrane $\geq$ 50%, retinal angiomatous proliferation (RAP), presumed ocular histoplasmosis	• Known hypersensitivity to the study medication, its components, or medications with a similar chemical structure. • Pregnant or breastfeeding women. • History of stroke or myocardial infarction. • Ongoing treatment for systemic infection. • Known allergy to fluorescein.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	syndrome (POHS), chorioretinal anastomosis (CRA), myopic CNV, CNV secondary to trauma, uveitis, CSCR, or other causes besides AMD. • Pigment epithelial tear. • Subretinal fibrosis or choroidal/choriocapillaris atrophy. • Previous focal subfoveal laser coagulation in the study eye. • Juxta- or extrafoveal laser coagulation within 1 month prior to Day 1. • Previous vitrectomy. • Prior surgery for macular degeneration. • Other ocular conditions deemed by the investigator to require surgery during the study period or likely to cause a loss of 2 lines of vision during the study (e.g., cataract). • Acute intraocular inflammation. • Vitreous hemorrhage. • Macular hole. • Diabetic retinopathy. • Previous retinal detachment. • Aphakia or pseudophakia with a defective posterior capsule (exception: post-YAG capsulotomy). • Myopia exceeding -8 diopters. • Previous intraocular surgery in the study eye within 2 months prior to Day 1. • Uncontrolled glaucoma with intraocular pressure $\geq$ 30 mmHg despite medication. • Previous filtering glaucoma surgery. • Previous corneal transplantation. **Either eye** • Uveitis. • Acute conjunctivitis, keratitis, scleritis, or endophthalmitis. **Non study eye** • Treatment of the fellow eye with verteporfin within 7 days prior to Day 1. **Other** • Glaucoma patients treated with prostaglandin-containing eye drops.	• Insufficient fundus. documentation quality due to poor visualization.
Galvez et al. 2020	**Study eye** • Central fibrosis preventing recovery of visual acuity (VA); structural damage within half a disc diameter from the centre of the macula • Other ocular diseases such as aphakia, pseudoexfoliation; severe vitreous haemorrhage, rhegmatogenous retinal detachment, proliferative diabetic retinopathy • Active periocular or ocular inflammation/ infection • Uncontrolled glaucoma with intraocular pressure (IOP) $\geq$30 mm Hg under therapy; • Neovascularization of the iris or neovascular • Glaucoma • History of any intraocular procedure within the previous 2 months • Treatment with intraocular or peribulbar corticosteroids in the study eye within the previous 6 months **Either eye** • CNV from any cause other than nAMD. **Other** • Treatment with systemic anti-VEGF agents (e.g. bevacizumab) within the previous 6 months.	• History of stroke or myocardial infarction within the previous 6 months. • Uncontrolled systolic blood pressure of more than 160 mm Hg or diastolic blood pressure of more than 100 mm Hg. • Current treatment with drugs that can be toxic to the retina and/or optic nerve. • Women of childbearing potential not using effective contraception methods.
Gillies et al. 2019	**Study eye.** • Treatment with any anti-angiogenic drugs (including any anti-VEGF agents) prior to Baseline. • Intra or periocular corticosteroids (including sub tenon but excluding topical formulations) • Structural damage within 0.5 disc diameter of the centre of the macula (e.g. vitreomacular traction, epiretinal membrane, scar, laser burn, foveal atrophy) at the time of screening that in the investigator's opinion could preclude visual function improvement with treatment. Exclusion criteria for prior or current systemic medication: • Intraocular corticosteroid implants Treatment with any anti-angiogenic drug (including any anti-VEGF agents) is allowed prior to Baseline in fellow eye. • Any intraocular procedure (including Yttrium-Aluminium-Garnet capsulotomy) within 2 months prior to Baseline or anticipated within the next 6 months following Baseline.	• Pregnant or nursing (lactating) women. • Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg at Screening or Baseline. • Any type of systemic disease or its treatment, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the participant to a significant degree or put the participant at special risk. • Stroke or myocardial infarction less than 3 months prior to screening. • Known hypersensitivity to ranibizumab or aflibercept or any component of the ranibizumab or aflibercept formulation, or fluorescein. Exclusion criteria for ocular medical history and conditions. • Use of other investigational drugs within 30 days or 5 half-lives from baseline, whichever is longer. • Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve as outlined in the study treatments.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	Visually significant cataract (likely to require surgery within the next 12 months), aphakia, severe vitreous haemorrhage, rhegmatogenous retinal detachment, proliferative diabetic retinopathy or CNV of any cause other than nAMD (e.g., ocular histoplasmosis, pathologic myopia macular hole) at the time of Screening and Baseline. **Either eye** • Any active periocular or ocular infection or inflammation (e.g. blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline. • One or more patches of geographic atrophy $>$ 250μm in longest linear dimension. • Uncontrolled glaucoma (intraocular pressure $\geq$30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline. • Neovascularisation of the iris or neovascular glaucoma at the time of Screening or Baseline.	
Gragoudas et al. 2004	**Study eye** • Patients with a history of previous subfoveal thermal laser therapy. • Patients with a history of up to one photodynamic therapy (PDT) treatment were eligible only if the PDT treatment occurred between 8 and 13 weeks prior to the baseline visit. • Likelihood of requiring cataract surgery within 2 years • Other potential causes of CNV, including myopia of 8 diopters or more or axial length of 25 mm or more, ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis. • Any intraocular surgery within 3 months or extrafoveal/juxtafoveal laser within 2 weeks of study entry. • Previous posterior vitrectomy or scleral buckling surgery. • Presence of retinal pigment epithelial tears or rips. • Patients also were excluded if they had diabetic retinopathy. • Acute ocular or periocular infection. **Other** • Concomitant therapy with any investigational agent to treat AMD (except vitamins and minerals) were excluded.	• History or evidence of severe cardiac disease (New York Heart Association functional class III or IV); a myocardial infarction within 6 months; ventricular tachyarrhythmia requiring ongoing treatment or unstable angina; a 3 history or evidence of peripheral vascular disease stroke within 12 months of study entry. • Previous therapeutic radiation to the eye, head, or neck. • Any treatment with an investigational agent in the past 60 days for any condition. • Known serious allergies to fluorescein dye (and indocyanine green, if used) or to components of the pegaptanib formulation.
Heier et al. 2012	**Study eye** • Any prior ocular or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins. • Prior treatment with anti VEGF therapy is not allowed. • Any prior or concomitant therapy with another investigational agent to treat neovascular AMD, except dietary supplements or vitamins. • Presence of retinal pigment epithelial tears or rips involving the macula. • History of any vitreous hemorrhage within 4 weeks prior to Visit 1.. • Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis. Prior vitrectomy. • History of retinal detachment or treatment or surgery for retinal detachment. • Any history of macular hole of stage 2 and above. • Any intraocular or periocular surgery within 3 months of Day 1, except lid surgery, which may not have taken place within 1 month of day 1, as long as its unlikely to interfere with the injection. • Prior trabeculectomy or other filtration surgery. • Uncontrolled glaucoma (defined as intraocular pressure $\geq$ 25 mmHg despite treatment with antiglaucoma medication). • Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium aluminum garnet [YAG] posterior capsulotomy) . • Previous therapeutic radiation in the region. • History of corneal transplant or corneal dystrophy. • Any concurrent intraocular condition (e.g. cataract) that, in the opinion of the investigator, could require either medical or surgical intervention during the 96 week study period. • Any concurrent ocular condition which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of intraocular injection, or which otherwise may	• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications. • The use of long acting steroids, either systemically or intraocularly, in the 6 months prior to day 1. • Any history of allergy to povidone iodine. • Known serious allergy to the fluorescein sodium for injection in angiography. • Presence of any contraindications indicated in the FDA Approved label for ranibizumab (Lucentis®; Genentech Inc., South San Francisco, CA). • Females who are pregnant, breastfeeding.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	interfere with the injection procedure or with evaluation of efficacy or safety. **Either eye** • Prior treatment with anti-VEGF agents. • History or clinical evidence of diabetic retinopathy, diabetic macular edema or any other vascular disease affecting the retina, other than AMD, in either eye. • Active intraocular inflammation. • Active ocular or periocular infection • Any ocular or periocular infection within the last 2 weeks prior to Screening. • Any history of uveitis. • Presence or history of scleromalacia. **Non study eye** • Prior treatment with anti VEGF therapy with an investigational agent (not FDA approved, e.g. bevacizumab) is allowed up to 3 months prior to first dose in the study, and such treatment will not be allowed during the study. • Prior treatment with an FDA/Health Canada approved anti VEGF therapy is allowed. • Prior systemic anti VEGF therapy, investigational or FDA/Health Canada approved, is only allowed up to 3 months prior to first dose, and will not be allowed during the study. **Other** • Significant media opacities, including cataract, in the study eye that might interfere with visual acuity, assessment of safety, or fundus photography. • Any systemic or ocular treatment with an investigational agent in the past 12 weeks prior to Day 1.	
Heier et al. 2022	**Study eye** • CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis. • Any history of macular pathology unrelated to AMD affecting vision or contributing to the presence of intraretinal or subretinal fluid. • Presence at screening of central serous chorioretinopathy • Retinal pigment epithelial tear involving the macula on day 1. • Any concurrent intraocular condition (eg, amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study. • Current vitreous haemorrhage on day 1. • Uncontrolled glaucoma • Spherical equivalent of refractive error demonstrating >8 diopters of myopia. • For patients who have undergone previous refractive or cataract surgery, the preoperative refractive error should not have exceeded −8 diopters of myopia. • Any cataract surgery or treatment for complications of cataract surgery with steroids or YAG laser capsulotomy within 3 months before day 1. • Any other intraocular surgery (e.g., pars plana vitrectomy, glaucoma surgery, corneal transplant, or radiotherapy). **Either eye** • Previous administration of IVT faricimab. • Previous periocular pharmacological or IVT treatment (including anti-VEGF medication) for other retinal diseases • Any prior or concomitant treatment for CNV or vitreomacular-interface abnormalities, including, but not restricted to, IVT treatment (eg, anti-VEGF, steroids, tissue plasminogen activator, ocriplasmin, C3F8, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or ocular surgical intervention. • Any history of idiopathic or autoimmune-associated uveitis in either eye Active ocular inflammation or suspected or active ocular or periocular infection in either eye on day 1 **Non-study eye** • Non-functioning non-study eye, defined as either no physical presence of non-study eye (ie, monocular)	• Any major illness or major surgical procedure within 1 month before screening. • Active cancer within the past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, and prostate cancer with a Gleason score of 12 months. • Requirement for continuous use of any medications and treatments indicated as prohibited therapy. • Systemic treatment for suspected or active systemic infection on day 1. • Ongoing use of prophylactic antibiotic therapy may be acceptable if approved after discussion with the medical monitor. • Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg whilst a patient is at rest on day 1. • If a patient's initial reading exceeds these values, a second reading may be obtained later the same day or on another day during the screening period. If the patient's blood pressure is controlled by anti-hypertensive medication, the patient should be taking the same medication continuously for ≥30 days before day 1. • Stroke (cerebral vascular accident) or myocardial infarction within 6 months before day. • History of other disease, metabolic dysfunction, physical examination finding, or historical or current clinical laboratory finding giving reasonable suspicion of a condition that contraindicates the use of the investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk for treatment complications in the opinion of the investigator. • History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of faricimab or to aflibercept injections, study-related procedure preparations (including fluorescein), dilating drops, or any of the anaesthetic and anti-microbial drops used by the patient during the study.
Holz et al. 2022	**Study eye**	• Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives from screening, whichever was longer.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• Prior treatment with verteporfin (PDT), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation). • History of vitrectomy, macular surgery, or other surgical intervention for AMD. • History of IVT or periocular injections of corticosteroids or device implantation within 6 months before screening. • Topical ocular corticosteroids administered for at least 30 consecutive days within 3 months before screening • Any other intraocular surgery (including cataract surgery) in the study eye within 3 months before screening • Retinal pigment epithelial tear involving the macula. • History of full-thickness macular hole (stage 2 and above by clinical examination or full-thickness macular hole by SD-OCT imaging of any size). • History of retinal detachment. • Current vitreous hemorrhage. • Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia • For patients who had undergone prior refractive or cataract surgery the preoperative refractive error in the study eye could not exceed 8 diopters of myopia. • History of corneal transplant. • Aphakia. Absence of an intact posterior capsule was allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation. • Active or recent (within 4 weeks) intraocular inflammation of clinical significance such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis, or endophthalmitis. • Uncontrolled hypertension or glaucoma (defined as intraocular pressure $\geq$30 mm Hg, despite treatment with antiglaucomatous medication). • Ocular disorders (i.e., retinal detachment, preretinal membrane of the macula, or cataract with significant impact on visual acuity) at the time of enrollment that could have confounded interpretation of study results and compromised visual acuity • Any concurrent intraocular condition (e.g., glaucoma, cataract, or diabetic retinopathy) that, in the opinion of the Investigator, would either have required surgical intervention during the study to prevent or treat visual loss that might have resulted from that condition or affect interpretation of study results. **Either eye** • Any prior treatment with IVT anti-VEGF agent (e.g., bevacizumab, aflibercept, ranibizumab). **Non-study eye** • Any diagnosis and/or signs of nAMD requiring treatment with an IVT anti-VEGF agent (e.g., aflibercept, bevacizumab, ranibizumab) within the screening period or at study treatment initiation (visit 1). **Other** • Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines, and ethambutol.	• Any type of advanced, severe, or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it might have biased the assessment of the clinical status of the patient to a significant degree or put the patient at special risk. • Stroke or myocardial infarction within 3 months before screening. • Presence of uncontrolled systolic blood pressure >160 mm Hg or uncontrolled diastolic blood pressure >100 mm Hg. • Known hypersensitivity to the investigational drug (ranibizumab or any component of the ranibizumab formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation. • History of recurrent significant infections and/or current treatment for active systemic infection. • Pregnancy or lactation. • Systemic treatment with high doses of corticosteroids (administration of >10 mg/day of prednisolone equivalent) during the last 6 months before screening.
Kertes et al. 2019	**Study eye** • Structural foveal damage, confounding severe ocular disease. • Clinical suspicion of polypoidal choroidal vasculopathy. • Patients who had any prior treatment, e.g., with Visudyne, Avastin, prior Ranibizumab treatment, Ozurdex*, external radiation therapy, transpupillary thermotherapy (TTT), or any intravitreal injection. • Patients who had previous subfoveal laser photocoagulation. **Either eye** • Active or suspected ocular or periocular infections. • Active intraocular inflammation. **Other** • Patients having received systemic treatment with any other anti-vascular endothelial growth factor (VEGF) therapy $\leq$ 60 days prior to enrollment	• Patients with a known sensitivity to Ranibizumab or any component of its formulation. • Patients physically unable to tolerate intravenous fluorescein angiography. • Any patient with recent history of new onset cardiac disease or thromboembolic central nervous system (CNS) event (within 12 months of Baseline Visit). • Patients with any other condition which, in the opinion of the Investigator, would require treatment that would significantly impact the treatment assessments during this study.
Khanani et al. 2020	**Study eye** • Prior IVT treatment (including anti-VEGF medication) except for management of cataract complication with steroid IVT treatment.	• Any major illness or major surgical procedure within 1 month before screening. • Uncontrolled blood pressure (defined as systolic >180 mm Hg and/or diastolic >100 mm Hg while participant at rest). If a participant's initial reading exceeded these values, a second reading was taken later on the

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis. • Central serous chorioretinopathy at screening. • Retinal pigment epithelial tear involving the macula. • Any prior or concomitant treatment for CNV including (but not restricted to) IVT treatment (steroids, anti-VEGF, tissue plasminogen activator, ocriplasmin, C3F8 gas, air), periocular pharmacological intervention, argon laser photocoagulation, verteporfin photodynamic therapy, diode laser, transpupillary thermotherapy, or surgical intervention. • Cataract surgery within 3 months of baseline assessments (day 1) • Any other intraocular surgery (pars plana vitrectomy, glaucoma surgery, corneal transplant, radiotherapy) • Prior periocular pharmacological intervention for other retinal diseases • Any concurrent intraocular condition (eg, amblyopia, aphakia, retinal detachment, cataract, diabetic retinopathy or maculopathy, or epiretinal membrane with traction) that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the course of the study. • Active intraocular inflammation (grade trace or above) on day 1 (before randomization) • Current vitreous hemorrhage • Uncontrolled glaucoma (eg, progressive loss of visual fields or defined as IOP $\geq$25 mm Hg despite treatment with antiglaucoma medication). • Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia. **Either eye** • History of idiopathic or autoimmune-associated uveitis • Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye on day 1 (before randomization)	same day, or on another day during the screening period. If the participant's blood pressure was controlled by antihypertensive medication, the participant was taking the same medication continuously for at least 30 days before day 1. • Stroke or myocardial infarction within 3 months before day 1. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory findings giving reasonable suspicion of a condition that contraindicated the use of the investigational drug or that might affect interpretation of the results of the study or renders the participant at high risk for treatment complications in the opinion of the investigator. • Pregnant or breastfeeding. • Known hypersensitivity to ranibizumab, fluorescein, any ingredients of the formulation used, dilating eye drops, or any of the anesthetic and antimicrobial drops used. • Treatment with investigational therapy within 3 months before initiation of study treatment.
Krebs et al. 2013	**Study eye** • Prior treatment with verteporfin photodynamic therapy. • Prior treatment with any intravitreal drug in the study eye. • Choroidal neovascularisation in either of the two eyes due to causes other than age-related macular degeneration such as histoplasmosis or pathological myopia (refractive error in the study eye demonstrating more than –6 dioptres or an axial length of $\geq$26 mm of myopia). • Laser photocoagulation within 1 month before study entry in the study eye. • Retinal pigment epithelial tear involving the macula in the study eye. • History of uncontrolled glaucoma in the study eye (defined as intraocular pressure $\geq$25 mm Hg despite treatment with topical antiglaucomatous medication). • Any concurrent intraocular condition in the study eye that could either require medical or surgical intervention during the 12-month study period or that could contribute to a loss of best corrected visual acuity over the 12-month study period (eg, diabetic retinopathy, cataract, uncontrolled glaucoma). The decision on exclusion is to be based on the opinion of the local principal investigator. • Active intraocular inflammation. • Vitreous haemorrhage in the study eye. • History of rhegmatogenous retinal detachment or stage 3 or 4 macula hole in the study eye. • Aphakia or absence of the posterior capsule in the study eye. • Intraocular surgery in the study eye within 2 months before the entry of the study • History of corneal transplant in the study eye **Either eye** • Prior treatment with systemic bevacizumab. • Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis on day 1 (before randomization). • History of idiopathic or autoimmune-associated uveitis. • Acute or recurrent infectious conjunctivitis, keratitis, scleritis or endophthalmitis. **Non-study eye** • Prior treatment with any intravitreal drug or verteporfin photodynamic therapy within the 3 months before the study entry.	• Pregnancy (a pregnancy test will be done monthly in women of childbearing potential). • History of myocardial infarction and/or stroke. • History of any ocular or systemic disease that according to the opinion of the local principal investigator may affect the interpretation of the study results or render the subject at high risk for treatment complications including severe hypertension. • History of allergy to fluorescein, not amendable with diphenhydramine.
Kunimoto et al. 2020	**Study eye** • Presence of CNV other than AMD at screening, e.g., pathologic myopia, ocular histoplasmosis, and angioid streaks.	• Females who are pregnant, nursing. • History or current evidence of hypersensitivity to any component of the study medication, or clinically relevant sensitivity to fluorescein, as assessed by the investigator at screening.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• Previous use of verteporfin PDT or any ocular anti-angiogenic therapy, approved or investigational, for the treatment of neovascular AMD, or previous therapeutic radiation in the region of the study eye. • Spherical equivalent of −8 diopters of myopia or worse (prior to cataract or refractive surgery) at screening • Any active iris neovascularization, or current evidence of vitreous hemorrhage or retinal detachment (considered by the investigator to significantly affect central vision) prior to baseline • Previous or concurrent macular laser treatment • Presence of an RPE tear or rip lesion involving the macula as assessed by the investigator at screening and confirmed by the CRC prior to baseline • Structural damage to the center of the macula that is likely to preclude improvement in BCVA as assessed by the investigator at screening and confirmed by the CRC prior to baseline, including any of the following: – Macular hole stage 3 or 4 – Atrophy of the RPE – Retinal fibrosis or scarring. • Vitreomacular traction or epiretinal membrane, as assessed by the investigator to significantly affect central vision at screening, and confirmed by the CRC prior to baseline. • History or evidence of any of the following surgeries: – Pars plana vitrectomy – Submacular surgery or other surgical intervention for AMD – Incisional glaucoma surgery – Cataract or refractive surgery (excluding YAG laser posterior capsulotomy) within the last 3 months prior to baseline. • Uncontrolled glaucoma or ocular hypertension (defined as IOP ≥25 mmHg despite treatment with ocular hypotensive medications) at screening and confirmed at baseline. • Aphakia or absence of the posterior capsule, or violation of the posterior capsule, unless the violation occurred as a result of YAG laser posterior capsulotomy, performed more than 1 month before baseline. • Any concurrent ocular or intraocular condition which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from the standard procedure of intraocular injections, or which otherwise may interfere with the injection procedure or evaluation of efficacy or safety. **Either eye** • Prior use of ocular anti-VEGF agents for neovascular eye diseases other than AMD • Active periocular, ocular, or intraocular infection at baseline. • History of recurrent or currently active ocular or intraocular inflammation at baseline. • History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than AMD at screening. **Other** • Treatment with systemic anti-VEGF medication (e.g., bevacizumab, ziv-aflibercept) or VEGFreceptor inhibitor (e.g., sunitinib, sorafenib, pazopa-nib) within 3 months prior to baseline • Any prior or current systemic or ocular treatment (including surgery) for neovascular AMD, approved or investigational, except dietary supplements or vitamins. • Treatment with ocular corticosteroid injections or implants within 6 months prior to baseline, or with fluocinolone acetonide implant within 36 months prior to baseline 2	• History or current evidence of hypersensitivity, allergy, or anaphylactic reaction to povidone iodine solution, as assessed by the investigator at screening. • History or current evidence of a medical condition that may, in the opinion of the investigator, preclude the safe administration of study medication, adherence to the scheduled study visits, or safe participation in the study, or that may confound the study results. • Use of systemic (e.g., oral, intravenous, intramuscular, rectal), or extensive dermal (>20% of total body surface area) corticosteroids within 5 days prior to baseline.
Lanzetta et al. 2024	Study eye • Causes of CNV other than nAMD. • Presence of retinal pigment epithelial tears or rips involving the centre subfield.. • Uncontrolled glaucoma (defined as intraocular pressure [IOP] >25 mmHg despite treatment with antiglaucoma medication). • History of idiopathic or autoimmune uveitis. • Vitreomacular traction or epiretinal membrane evident on biomicroscopy or OCT that is thought to affect central vision. • Any history of macular hole of stage 2 and above. • Structural damage to the center of the macula that is likely to preclude improvement in BCVA following the resolution of retinal fluid including, but not limited to, atrophy of the retinal pigment epithelium, subretinal fibrosis or scar or significant macular ischaemia. • History of, or likely future need of, filtration or tube shunt surgery. • Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminumgarnet [YAG] posterior capsu-lotomy performed more than 30 days before screening). • Myopia of a spherical equivalent of at least 8 dioptres prior to any refractive or cataract surgery.	• Uncontrolled blood pressure (blood pressure [BP]; defined as systolic >160 mmHg or diastolic >95 mmHg). • Participants may be treated with up to three agents known to have antihypertensive effects for arterial hypertension to achieve adequate BP control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the participant was not for BP control. • Any recent changes in medications known to affect BP need to be stable for 12 weeks prior to screening. • History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of the screening visit. • Renal failure requiring dialysis, or renal transplant at screening or potentially during the study. • Allergy or hypersensitivity to any of the compounds/excipients in the study interventions formulations. • Presence of any contraindications indicated in the locally approved label for aflibercept. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, might affect interpretation of the results of the study, or renders the participant at high risk for treatment complications.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• Significant media opacities, including cataract, that interfere with BCVA assessment, fundus photography, or OCT imaging. • History of corneal transplant or corneal dystrophy. • History of irregular astigmatism or amblyopia with chronic limitation of BCVA. • Any prior or concomitant ocular (in the study eye) or systemic treatment (with an investigational or approved, anti-vascular endothelial growth factor [VEGF] or other agent) or surgery for nAMD, except dietary supplements or vitamins. • Prior treatment of the study eye with any of the following drugs (any route of ophthalmic administration) or procedures before baseline visit (day 1). • Vitreoretinal surgery and/or including scleral buckling at any time. • Any other intraocular surgery within 90 days before the screening visit. Page 11 of 18 f. Panretinal laser photocoagulation or macular laser photocoagulation within 90 days of the screening visit. • YAG capsulotomy in the study eye within 30 days of the screening visit. **Either eye** • Prior or concomitant conditions: History or clinical evidence of diabetic retinopathy, diabetic macular oedema, or any retinal vascular disease other than nAMD. • Evidence of extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) at the time of screening/randomisation. • Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit. • Prior treatment of the fellow eye with any of the following: • Investigational therapy (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies) within 180 days of the screening visit. • Intravitreal implant, gene therapy, or cell therapy at any time. • Prior treatment in the fellow eye with approved anti-VEGF therapy is allowed. • Prior treatment in the fellow eye with bevacizumab (although not approved but a component of standard of care in some countries) is also allowed. **Non-study eye** • Ocular conditions with poorer prognosis. **Other** • Anti-angiogenic drugs at any time including investigational therapy (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies).	• Pregnant or breastfeeding women. • Long-acting steroids within 16 weeks (112 days) of the screening visit, or any treatment with intravitreal implant, gene therapy, or cell therapy at any time. • Ocriplasmin (Jetrea®) at any time.
Li et al. 2014	**Study eye** • Significant subfoveal atrophy or scarring • Previous laser therapy or other ocular operation, or both, in the study eye, such as macular translocation surgery, cataract surgery, vitrectomy surgery, glaucoma filtering operation, verteporfin photodynamic therapy, subfoveal focal laser photocoagulation, and transpupillary thermotherapy. **Either eye** • History of previous AMD drug treatment (such as anti-VEGF drugs and steroids) • Presence of other causes of CNV. • Active ocular inflammation or Infection.	• Uncontrolled diabetes mellitus. • Uncontrolled hypertension. • History of cerebrovascular accident or myocardial infarction within 6 months. • Renal failure requiring dialysis or renal transplant. • Pregnancy or lactation. • History of allergy to fluorescein or povidone iodine.
Li et al. 2024	**Study eye:** • Scar, fibrosis, atrophy that involved the center of the fovea, or subfoveal hard exudate • Choroidal neovascularization secondary to other reasons, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture, or pathologic myopia • Any ocular abnormality affecting visual acuity or macular examination • Current vitreous haemorrhage within 30 days before randomization • Any other intraocular surgery or periocular surgery within 90 days prior to randomization, except for lid surgery, which may not have taken place within 30 days prior to randomization. • Uncontrolled ocular hypertension (defined as intraocular pressure $\geq$25 mmHg despite treatment with anti-glaucoma medication) at screening **Either eye** • Any previous intravitreal anti-vascular endothelial growth factor treatment • History of treatment involving macula such as macular laser photocoagulation, photodynamic therapy, transpupillary thermotherapy,	• Known allergic reactions and/or hypersensitivity to any component of Eylea® or QL1207 or allergy to the fluorescein sodium for injection in angiography. • Uncontrolled systemic hypertension (systolic blood pressure $\geq$160 mmHg and/or diastolic blood pressure $\geq$95 mmHg on optimal medical regimen). • Uncontrolled clinical conditions (such as severe mental, neurological, cardiovascular, respiratory, urinary disorders as well as malignancies); • Myocardial infarction and/or cerebral infarction within 180 days prior to the first dose. • Any previous systemic anti-vascular endothelial growth factor treatment. • Women of childbearing potential who are pregnant. • Systemic autoimmune diseases. • Patients with hepatitis B (HbsAg-positive and HBV-DNA shows viral replication). • Patients with hepatitis C (anti-HCV antibody positive and HCV-RNA shows viral replication). • Patients who test positive for syphilis (positive treponemal test; except for patients with negative nontreponemal test and confirmed inactive infection based on clinical judgment). • Patients with a known history of HIV-positivity or positive HIV screening test.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	radiation therapy, or any ocular treatment for neovascular age-related macular degeneration • Active or suspected ocular and periocular infection at screening or at randomization • History of idiopathic or autoimmune-associated uveitis	
Loewenstein et al. 2023	**Study eye** • Any previous vitreoretinal surgery for any cause. • Topical ocular corticosteroids administered for $\geq$ 30 consecutive days within 90 days prior to Screening. • Spherical equivalent of the refractive error in the demonstrating more than 8 diopters of myopia. • Corneal transplant or corneal dystrophy. • History of rhegmatogenous retinal detachment. • History of macular hole. • Retinal pigment epithelial tear or rip, involving the macula as assessed by FA and confirmed by the central reading center. • Current vitreous hemorrhage. • Other intraocular surgery (including cataract surgery) within the 3 months prior to baseline. The yttrium aluminum garnet [YAG] posterior capsulotomy is allowed not later than 4 weeks prior to screening. • Any concurrent intraocular condition (eg, cataract or diabetic retinopathy) that, in the opinion of the investigator, could require treatment during the study period to prevent or treat loss of visual acuity. • Significant media opacities (including cataract) in the study eye interfering with BCVA assessment or fundus imaging (FA/FP/OCT). • Aphakia or absence of the posterior capsule unless it occurred as a result of a YAG posterior capsulotomy in association with prior posterior chamber intraocular lens implantation. • Presence of advanced glaucoma or optic neuropathy that involve(s) or threaten(s) the central visual field (as judged by the investigator). • History of glaucoma filtering surgery or argon laser trabeculoplasty (Exception: Laser iridotomy and selective laser trabeculoplasty are allowed). • Uncontrolled ocular glaucoma or hypertension, defined as IOP $\geq$ 25 mmHg despite treatment with anti-glaucoma medication. **Either eye** • Any previous intervention including pharmacological treatment, laser and/or surgery for wAMD (Exception: Vitamin supplementation for AMD prevention). • Any previous IVT treatment including any anti-VEGF medications, steroids and/or any other investigational medication. • Choroidal neovascularization in due to non-AMD causes (eg, DME, RVO, ocular histoplasmosis or trauma, etc.) as assessed by FA and confirmed by central reading center. • Active or recent (within 28 days prior to randomization) intraocular, extraocular, and periocular inflammation or infection. • History of idiopathic or autoimmune-associated uveitis. • Infectious conjunctivitis, keratitis, scleritis or endophthalmitis. **Non-study eye** • Should not be expected to need any anti-VEGF treatment for the duration of study participation. **Other** • The use of long-acting steroids, either systemic or intraocular in any eye, in the 18 months before planned initiation of study treatment. (Note: Iluvien® [fluocinolone acetonide intravitreal], current or planned implantation during the study, is prohibited.)	• Contraindication for Lucentis® (hypersensitivity to ranibizumab or to any of the study treatment excipients). • Current treatment for active systemic infection.
Lushchyk et al. 2013	**Study eye** • If any other significant ocular disorders affecting visual acuity were present. • Patients had an ocular surgery planned during the 1-year follow-up period.	• Allergy to either FA or ICG dye injections was known. • Patients who used coumarin derivatives at the time of inclusion and patients who experienced clinically significant cerebrovascular accident or myocardial infarction in the 6 months prior to planned inclusion were ineligible for this study.
Mahmood et al. 2015	**Study eye** • Prior treatment to the CNV lesion. • Retinal pigment epithelial tear (rip). • Active intraocular inflammation within one month of screening for study • Active or suspected ocular or periocular infection • Uncontrolled glaucoma in study eye (IOP of greater than 25 mmHg despite anti-glaucomatous medication) • History of ocular surgery or YAG (yttrium aluminium garnet) laser capsulotomy within two months of screening for study	• History of allergy to fluorescein. • Any systemic medication that may interfere with the safety of the patient or is known to be toxic to the retina. • Uncontrolled hypertension • Within one month of major surgery. • History of myocardial infarction, stroke or gastrointestinal perforation. • Episode of angina or transient ischaemic attack within 6 months of screening. • Pregnant and or lactating women.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
Martin et al. 2011	**Study eye** • Previous treatment with verteporfin PDT, Macugen™, LucentisTM, intravitreal Avastin®, thermal laser, external beam radiation or other AMD therapy. • History of submacular surgery or other surgical intervention for AMD. • Any concurrent intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 3 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 3 year follow-up period. • Active or recent (within 4 weeks) intraocular inflammation (grade trace or above). • Current vitreous hemorrhage. • History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4). • Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia. • For subjects who have undergone prior refractive or cataract surgery, the preoperative refractive error in the study eye cannot exceed 8 diopters of myopia. • Intraocular surgery (including cataract surgery) within 2 months preceding the first study treatment. • Uncontrolled glaucoma (defined as intraocular pressure >25 mmHg despite treatment with antiglaucoma medication). • Patients with other ocular diseases that can compromise the visual acuity such as amblyopia and anterior ischemic optic neuropathy • Patients with other progressive retinal disease likely to affect visual acuity within the next 3 years. **Either eye** • Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis. **Non-study eye** • Concurrent treatment with an investigational drug or device. **Other** • Previous treatment with intravenous Avastin® • Concurrent use of systemic anti-VEGF agents. • Patients who are unable to be photographed to document CNV, due to known allergy to fluorescein dye, lack of venous access or cataract obscuring the CNV.	• Pregnancy or lactation. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. • Current treatment for active systemic infection. • Evidence of significant uncontrolled concomitant diseases such as cardiovascular disease, nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders. • History of recurrent significant infections or bacterial infections
Menon et al. 2013	**Study eye** • Retinal vascular disease • Other retinal conditions that may effect visual outcome • Other sources of chorodal neovascular membrane • Previous PhotoDynamic Therapy (PDT) • Predominantly classic membranes • Glaucoma (IntraOcular Pressure [IOP] >25, on anti-glaucoma treatment, glaucoma surgery) • Active intraocular or extraocular inflammation • Previous cataract surgery (within 6 months) • Aphakia	• Uncontrolled hypertension. • Patients on more than 3 antihypertensive medications. • Patients in whom a change in anti-hypertensive drug was initiated within 3 months preceding baseline visit. • Previous thrombembolic phenomenon. • On Warfarin or anticoagulants • Recent Myocardial Infarction (MI). • Recent major surgery (within 28 days). • Allergy to anti Vascular Endothelial Growth Factor (VEGF) medications. • Allergy to humanised monoclonal antibody.
Mishra et al. 2022	**Study eye** • Any fibrosis or geographical atrophy of central subfield • Any intra or periocular infection or inflammation • Any concurrent intraocular disease like diabetic retinopathy **Either eye** • If the patient had received any approved treatment for neovascular AMD other than micronutrient supplementation	• History of drug sensitivity/ allergic reactions to research interventions. • Stroke or myocardial infarction in the 90 days preceding to baseline visit.
Mitchell et al. 2021	**Study eye** • Had received prior ocular or systemic treatment or surgery for nAMD. • Intraocular pressure ≥25 mmHg in the study eye. • Any other ocular condition in the study eye that might impact vision were excluded. **Either eye** • Patients were excluded if they had prior or current use of anti-vascular endothelial growth factor therapy. • Patients with active infection or intraocular inflammation in either eye.	

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
Nunes et al. 2019	**Study eye** • Previous intraocular treatment. • Any sign of palpebral infection, • Ocular diseases that could present with low vision. • Intraocular surgery in the past 2 months, • Significant media opacity. • Spherical equivalence of -8.00 D or more.	• Allergy to fluorescein. • Any uncontrolled systemic disease or condition that could interrupt the 1-year follow-up.
Ohji et al. 2020	**Study eye** • Prior treatment with intraocular anti-VEGF agents, verteporfin photodynamic therapy. • Other laser. • Intraocular corticosteroids. • Surgical interventions (except cataract surgery at more than 30 days prior to screening). • Active or suspected infection in or surrounding the study eye. • Active severe intraocular inflammation. • Intraocular pressure $\geq$25 mmHg. • Ocular condition that might impact vision and confound study outcomes **Other** • Systemic use of anti-VEGF products within 3 months prior to study entry.	• History of allergy to aflibercept or allergy to study/treatment-related agents, including fluorescein, indocyanine green, povidone iodide, lidocaine, or antibiotic eye drops. • Women who are pregnant or lactating, or suspected to be pregnant. • Previous enrollment into the run-in phase of this study.
Regillo et al. 2008	**Study eye** • Prior treatment with verteporfin photodynamic therapy, external-beam radiation therapy, or transpupillary thermotherapy. • History of submacular surgery or other surgical intervention for AMD. • Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation). • Previous subfoveal focal laser photocoagulation. • Laser photocoagulation (juxtafoveal or extrafoveal) within one month preceding day zero. • History of vitrectomy surgery. • Retinal pigment epithelial tear involving the macula. • Any concurrent intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either (a) require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition, or (b) if allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of best-corrected visual acuity over the 24-month study period. • Active intraocular inflammation (grade trace or above). • Current vitreous hemorrhage. • History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4). • Aphakia or absence of the posterior capsule. • Previous violation of the posterior capsule was also a reason for exclusion unless it resulted from yttrium aluminum garnet (YAG) posterior capsulotomy in association with prior posterior chamber intraocular lens implantation. • Spherical equivalent of the refractive error demonstrating more than -8 diopters of myopia. For patients who underwent prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye could no exceed -8 diopters of myopia. • Intraocular surgery (including cataract surgery) within two months preceding day zero. • Uncontrolled glaucoma (defined as intraocular pressure of 30 mm Hg or more despite treatment with antiglaucoma medications. • History of glaucoma filtering surgery. • History of corneal transplant. **Either eye** • CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia • History of idiopathic or autoimmune-associated uveitis. • Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis. **Non–study eye** • Treatment with verteporfin photodynamic therapy in the nonstudy eye less than seven days preceding day zero. **Other** • Concurrent use of a systemic anti-VEGF agent, including treatment with intravitreal or intravenous bevacizumab.	• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. • Current treatment for active systemic infection. • History of allergy to fluorescein that is not amenable to treatment.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
Rosenfeld et al. 2006	**Study eye** • Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation). • History of submacular surgery or other surgical intervention for AMD. • Previous subfoveal focal laser photocoagulation. • Laser photocoagulation (juxtafoveal or extrafoveal) within 1 month preceding day 0. • History of vitrectomy surgery. • Retinal pigment epithelial tear involving the macula. • Any concurrent intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either (a) require medical or surgical intervention during the 24-month study period to prevent or treat visual loss that might result from that condition, or (b) if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 24-month study period. • Active intraocular inflammation (grade trace or above). • Current vitreous hemorrhage . • History of rhegmatogenous retinal detachment or macular hole (Stage 3 or 4). • Aphakia or absence of the posterior capsule. • Spherical equivalent of the refractive error demonstrating more than −8 diopters of myopia. • Intraocular surgery (including cataract surgery) within 2 months preceding day 0. • Uncontrolled glaucoma (defined as intraocular pressure of 30 mmHg or more despite treatment with antiglaucoma medications. • History of glaucoma filtering surgery. • History of corneal transplant. Either eye • CNV in due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia. • History of idiopathic or autoimmune-associated uveitis. • Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis. • Patients with angioid streaks or precursors of CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.	• History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications. • Current treatment for active systemic infection. • History of allergy to fluorescein, not amenable to treatment with diphenhydramine.
Schauwvlieghe et al. 2016	**Study eye** • Laser photocoagulation (juxtafoveal or extrafoveal) within one month preceding Baseline. • Spherical equivalent of refractive error in the study eye demonstrating more than– 8 dioptres of myopia. • Cataract extraction within three months preceding Baseline • IOP >25 mm Hg • Active intraocular inflammation. • Vitreous haemorrhage obscuring view of the posterior pole. • Presence of a retinal pigment epithelial tear involving the macula. **Either eye** • Ocular treatment with anti-angiogenic drugs in the last 2 months or Triamcinolone in the last 6 months. • Patients with angioid streaks or precursors of CNV due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.	• Systemic disease with a life expectancy shorter than the duration of the study. • History of hypersensitivity or allergy to fluorescein.
Schmidt-Erfurth et al. 2011	**Study eye** • Operative intervention for AMD in the past. • Laser photocoagulation within 1-month preceding baseline. • Clinically significant subretinal hemorrhage that involved the foveal center. • Prior treatment in the study eye with verteporfin, external-beam radiation therapy, subfoveal focal laser photocoagulation, vitrectomy, or trans-pupillary thermotherapy **Either eye** • Angioid streaks or precursors of CNV in either eye due to other causes.	• Any other significant clinical condition detrimental to the study outcome.
Scholler et al. 2014	**Study eye** • Prior treatment with any intravitreal drug. • Prior treatment with verteporfin photodynamic therapy. • Retinal pigment epithelial tear involving the macula. • Laser photocoagulation within 1 month before study entry. • Any concurrent intraocular condition that could either require medical or surgical intervention during the 12 month study period or that could contribute to a loss of best corrected visual acuity over the 12 months study	• History of allergy to fluorescein, not amendable with diphenhydramine. • History of myocardial infaraction and/or stroke.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	period (e.g. diabetic retinopathy, cataract, uncontrolled glaucoma). The decision on exclusion is to be based on the opinion of the local principal investigator. • Active intraocular inflammation. • Vitreous hemorrhage. • History of rhematogenous retinal detachment or stage 3 or 4 macula hole. • Aphakia or absence of the posterior capsule. • Intraocular surgery in within 2 months before the entry of the study • History of corneal transplant. **Either eye** • Prior treatment with systemic bevacizumab. • CNV due to causes other than AMD such as histoplasmosis or pathologica myopia. • History of idiopathic or autoimmune-asscoaited uveitis. • Infectious conjunctivitis, keratitis, scleritis or endophthalmitis. **Non-study eye** • Prior treatment with any intravitreal drug or verteprofin photodynamic therapy within the 3 moths before the study entry. **Other** • History of any ocular or systemic disease that according to the opinion of the local principal investiagtor may affect the interpretation of the study results or render the subject at high risk for treatment complications	
Silva et al. 2018	**Study eye** • Ocular disorders (i.e., retinal detachment, pre-retinal membrane of the macula, or cataract with significant impact on VA) at the time of enrollment that may confound interpretation of study results and compromise VA. • Uncontrolled glaucoma (intraocular pressure [IOP] ≥30 mmHg on medication or according to investigator's judgment). • History of focal/grid laser photocoagulation with involvement of the macular area at any time. • Presence of amblyopia or ocular disorders with final best-corrected vision. • History of treatment with any anti-angiogenic drugs (including any anti-vascular endothelial growth factor [VEGF] agents; e.g., bevacizumab [Avastin®] and aflibercept [Eylea®]) or verteporfin photodynamic therapy. • History of intravitreal treatment with corticosteroids within 6 months before screening. • History of intraocular surgery within 3 months before screening **Either eye** • Any active periocular or ocular infection or inflammation. **Other** • Use of any systemic anti-VEGF drugs within 3 months before screening (e.g., bevacizumab [Avastin®] and ziv-aflibercept [Zaltrap®]). • Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines, and ethambutol.	• Any type of advanced, severe, or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk 2. • Stroke or myocardial infarction within 3 months before screening 3. • Presence of uncontrolled systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg 4. • Known hypersensitivity to the investigational drug (ranibizumab or any component of the ranibizumab formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation. • Use of other investigational drugs (excluding vitamins and minerals) within 30 days or 5 half-lives from screening, whichever longer Use of any systemic anti-VEGF drugs within 3 months before screening (e.g., bevacizumab [Avastin®] and ziv-aflibercept [Zaltrap®]). • Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after contraception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
Taipale et al. 2020	**Study eye** • Periocular infection. • Previous or active diabetic retinopathy. • Retinal vein/artery occlusion. • Retinal tear/detachment, • Retinal necrosis, • Vitritis. • Endophthalmitis, • Vitreous haemorrhage, • Retinal phlebitis, • Optic neuritis, • Glaucoma of any type • Fundus laser photocoagulation • Myopia above "6.0 dioptres. • Eye surgeries during the previous six months,	• Hydrocephalus/intracranial pressure that increases intracranial expansion, alcohol abuse, thyroid disease with abnormal thyroid-stimulating hormone (TSH) levels. • Immunological systemic disease. • Use of other antineoplastic drugs. • Pulmonary embolism. • Myocardial or cerebral infarction during the previous six months, clinically.
Tano et al. 2010	**Study eye** • Previous treatment in the	

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	study eye with PDT with verteporfin, radiation therapy, macular laser photocoagulation, vitrectomy or transpupillary thermotherapy. **Other** • Previously participated in a clinical study involving antiangiogenic drugs (for either eye), or had participated in a clinical study of any investigational drugs (excluding vitamins and minerals) within 1 month preceding EXTEND-I study commencement.	
Wang et al. 2019	**Study eye** • Used to accept following treatments for wet AMD within 3 months or accept following treatments more than three times before baseline: a) Anti-angiogenesis drugs (pegaptanib, anibizumab, bevacizumab,VEGF-Trap, KH902; b) Anecortave acetate corticosteroidsc c) Protein kinase C inhibitors, squalamine, siRNA d) PDT treatment,external beam radiotherapy, local laser photocoagulation, vitrectomy, submacular surgery and transpupillary thermotherapy • Any intraocular surgery(including YAG laser) within 3 months before baseline or predicated within 6 months after baseline • Intraocular or periocular treatment of corticosteroids within 3 months before baseline • Uncontrolled glaucoma (under treatment [IOP] $\geq$ 30 mm Hg or depend on researchers) while screening and baseline • Neovascularization of iris and neovascular glaucoma while screening and baseline • With structure injury (including vitreous macular traction, epiretinal membrane involving in central fovea, subretinal fibroplasia, laser scar and central fovea atrophy) within 0.5 optic disc diameter to the central of macula while screening and baseline, which may harm the improvement of vision by treatment according to researchers. **Either eye** • Any causes led to choroidal neovascularization except Wet AMD (including CNV,central serous chorioretinopathy,ocular histoplazmoza and pathologic myopia) while screening and baseline. • Any active periocular and ocular infection and inflammation (including blepharitis, conjunctivitis, keratitis, scleritis, uveitis, intraocular inflammation) while screening and baseline. **Non-study eye** • Any anti-angiogenesis treatment(including anti-VEGF,like Lucentis,Avastin® and KH902) within 3 months before baseline **Other** • Any systemic anti-VEGF medication(as Avastin) use within 3 months before screening • Any medication systemic use toxic to lens, retina and optic nerve,including iron amine, chloroquine/chloroquine (Plaquenil ®), tamoxifen, phenothiazine and ethambutol	• Have Stroke and myocardial infarction within 3 months before screening.
Woo et al. 2023	**Other** • Any previous systemic anti-VEGF treatment. **Study eye** • Presence of CNV due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture, or pathologic myopia (confirmed by the central reading centre during Screening) • Presence of retinal pigment epithelial tears or rips involving the macula (confirmed by the central reading centre during Screening) • Presence of macular hole at any stage (confirmed by the central reading centre during Screening) • Any concurrent macular abnormality other than AMD which could affect central Ophthalmology. vision or the efficacy of IP including but not limited to epiretinal membrane, vitreomacular traction, macular telangiectasia, retinal vascular abnormality, etc. (confirmed by the central reading centre during Screening) • Any concurrent ocular condition which, in the opinion of the Investigator, could either confound the interpretation of efficacy and safety of IP (e.g., ocular media opacities such as significant cataract, optic neuropathy etc.) or require medical or surgical intervention during the study period. • Current vitreous haemorrhage. • History of treatment involving macula such as macular laser photocoagulation, PDT, TTT, radiation therapy, or any ocular treatment for neovascular AMD.	• Known allergic reactions and/or hypersensitivity to any component of Eylea® or SB15. • History of allergy to the fluorescein sodium for injection in angiography. • History of a medical condition that would preclude scheduled study visits or safe use of IP in the opinion of the Investigator (e.g., history of organ transplant, immunocompromised subject, etc.). • Uncontrolled systemic disease including but not limited to uncontrolled diabetes mellitus (in the opinion of the Investigator), uncontrolled systemic hypertension (systolic blood pressure $\geq$180 mmHg and/or diastolic blood pressure $\geq$100 mmHg on optimal medical regimen), or uncontrolled atrial fibrillation (resting heart rate $\geq$110 beats per minutes) at screening. • Stroke, transient ischaemic attacks, or myocardial infarction within 180 days prior to randomization. • History of recurrent significant infections and/or current treatment for systemic infection. • Severe renal impairment with dialysis or a history of renal transplant. • Malignancy (other than non-melanoma skin cancer) under treatment or with history of metastatic disease. • Women of childbearing potential who are pregnant. • Use of systemic corticosteroids for 30 or more consecutive days within 90 days prior to randomisation (inhaled steroid is permitted).

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• History of vitrectomy, scleral buckling (encircling), glaucoma filtration surgery, corneal transplantation, or pan-retinal photocoagulation. • Previous ocular (intraocular and peribulbar) corticosteroids injection/ implant within 1 year prior to randomization. • Topical ocular corticosteroids administered for $\geq$ 30 consecutive days or for $\geq$ 60 non-consecutive days within 90 days prior to randomization. • Any other intraocular surgery (including cataract surgery or Yttrium Aluminium Garnet [YAG] laser posterior capsulotomy in association with prior posterior chamber intraocular lens [IOL] implantation) or periocular surgery within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation. • Spherical equivalent of the refractive error demonstrating more than 6 diopters of myopia. For subjects who have undergone previous refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 6 diopters of myopia. • Aphakia or absence of the posterior capsule (unless it occurred as a result of a YAG laser posterior capsulotomy in association with prior posterior chamber IOL implantation) Study eye: Uncontrolled ocular hypertension (defined as IOP $\geq$25 mmHg despite treatment with anti-glaucoma medication) at Screening. • Previous radiation therapy near the region of the study eye **Either eye** • History or clinical evidence of diabetic retinopathy (except for mild nonproliferative diabetic retinopathy) or DME • Any previous IVT anti-VEGF treatment (e.g., bevacizumab, ranibizumab, aflibercept, pegaptanib, etc.) • Active or suspected ocular and periocular infection at Screening or at randomisation (e.g., infectious blepharitis, infectious conjunctivitis, infection in eyelid) • Active intraocular inflammation including scleritis at Screening or at randomisation • History of idiopathic or autoimmune-associated uveitis **Other** • Any systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD within 30 days prior to randomisation, and such treatment or therapy will not be allowed during the study period. However, dietary supplements, vitamins, or minerals will be allowed. • Current use of medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, ethambutol, at Screening and such medications will not be allowed during the study period.	
Wykoff et al. 2015	No information	
Wykoff et al. 2023	**Study eye** • Prior use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium). • Previous use of intraocular or periocular corticosteroids within 120 days of screening or treatment with an intravitreal steroid implant at any time. • Treatment with ocriplasmin at any time. • Yttrium-aluminum-garnet capsulotomy within 14 days of the screening visits. • History of vitreoretinal surgery (including scleral buckling). • Intraocular pressure (IOP) $\geq$25 mm Hg. • Any history of macular hole of stage 2 and above. • Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments. • Inability to obtain fundus photographs, fluorescein angiography (FA), or spectraldomain optical coherence tomography (eg, due to media opacity, allergy to fluorescein dye, or lack of venous access). • Any concurrent ocular condition that, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of intravitreal injections, or that otherwise may interfere with the injection procedure or with evaluation of efficacy or safety. **Either eye** • Evidence of CNV due to any cause other than nAMD.	• Uncontrolled diabetes mellitus in the opinion of the investigator. • Uncontrolled blood pressure (BP) (defined as systolic BP >140 mm Hg or diastolic BP >90 mm Hg). • Patients may be treated with up to 3 agents known to have antihypertensive effects for arterial hypertension to achieve adequate BP control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the patient was not for BP control. • Any recent changes in medications known to affect BP need to be stable for 90 days before the screening visit. • Variation by more than 10% in the 3 pre randomization BP measures recorded at the screening 1, screening 2, and randomization visits. • History of cerebrovascular accident or transient ischemic attack or myocardial infarction/acute coronary syndrome within 180 days of screening visit. • Renal failure, dialysis, or history of renal transplant. • Known sensitivity to any of the compounds of the study formulation. • Members of the clinical site study team or their immediate family, unless prior approval granted by the sponsor. • Pregnant or breastfeeding women. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications. • Any active, unresolved systemic infectious disease that, in the opinion of the investigator, would interfere with the patient's ability to complete the study.

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Table 4 (*continued*)

Study name	Exclusion criteria on ocular co-morbidities	Exclusion criteria on systemic co-morbidities
	• Evidence of diabetic macular edema (DME) or diabetic retinopathy (defined as >1 microaneurysm) in patients with diabetes. • Prior intravitreal investigational agents (eg, anti–angiopoietin-2 or antiVEGF bispecific monoclonal antibodies, gene therapy). • Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis. • Any intraocular inflammation or infection within 90 days of the screening visit. **Non-study eye** • Ocular conditions with poorer prognosis in the fellow eye. • History of corneal transplant or corneal dystrophy in study eye **Other** • Any prior systemic anti-VEGF administration.	• Any patient who had a documented positive PCR or serology test for SARS-CoV-2 could be enrolled provided that the patient (1) had recovered from COVID-19 (all COVID19–related symptoms and major clinical findings that could have potentially affected the safety of the patient should be resolved at baseline), and (2) had 2 negative results from a health authority–authorized nucleic acid amplification (PCR) test for COVID-19 taken at least 48 hours apart.

heterogeneity. For example, baseline BCVA values at which eyes were eligible were typically between minimum 18–50 ETDRS letters and maximum 69–78 ETDRS letters, although some studies did not impose an upper limit. It was estimated that more than half of patients with AMD were ineligible for the pivotal MARINA and ANCHOR trials, as those with BCVA worse than 24 letters (20/320 Snellen equivalent) were excluded[61]. The eligibility criteria of BCVA remained unchanged in the more recent trails, such as LUCERNE, TENAYA, and PULSAR, as summarized in Table 2. The larger heterogeneity in real-world data has an important influence on the discrepancy between results observed in RCTs and real-world clinical practice. For example, one large real-world study of 4,678 treatment-naïve eyes with neovascular AMD who underwent anti-VEGF therapy with up to 10-year follow-up data showed that eyes with BCVA at 80–90 ETDRS at baseline decreased in mean BCVA over time likely due to a ceiling effect[62]. It can be speculated that if studies systematically ignore those with a good baseline vision to avoid ceiling effect, while real-world clinical practice is getting increasingly better at diagnosing and treating nAMD earlier[63], we may see an increasing gap between results of the RCTs and the real-world data. On the other end of the spectrum, some of our patients are diagnosed very late, with poorer prognosis, and who may fail the RCT eligibility criteria for visual function or disease stage. In routine practice, these patients may be eligible for treatment within the framework of the healthcare system.

The criteria upon which neovascular AMD was diagnosed and evaluated changed over time as FA went from being the primary source of evaluation[7,8,15,16,47] to a more multimodal approach which included OCT (Table 3). Such temporal trends, which also reflect routine clinical practice, is supportive to the generalizability of these trials for the routine clinical practice.

Patients with nAMD are known to have a high rate of ocular and systemic comorbidities[64–66], presumed to coincide with overlapping risk factors and pathophysiological mechanisms such as ageing, inflammation, and oxidative stress[67–73]. Yet, the most frequent exclusion criteria across studies were any history of following: intraocular surgery, diabetic retinopathy, panretinal photocoagulation, glaucoma, and myopia. As glaucoma and nAMD are leading causes of vision loss in elderly individuals, patients with these conditions are often seen in clinical practice[66,74]. Similarly, an important number of patients with neovascular AMD also have retinal comorbidities such as diabetic retinopathy, uveitis, or retinal vein occlusion[66]. Cardiovascular disease accounts for nearly half of the non-communicable diseases and shares common risk factors with nAMD[75]. However, patients with cardiovascular disease were in general ineligible for the RCTs unless they were under optimal disease management or have not had any prior event, as summarized in Table 4. Omitting these patients may significantly underestimate the cardiovascular events in the RCTs. In one study of ocular and systemic comorbidities 26,057 Medicare beneficiaries with nAMD and a matched control group, it was reported that nearly all patients with nAMD had at least one comorbidity, and that >80 % had five or more comorbidities in the general disease categories[76]. Extensive exclusion criteria employed in the RCTs therefore reduce the generalizability to the more diverse population in real-world clinical settings. Further, it can be speculated that this lack of diversity of the study populations may create disparities in the rate of adverse events seen in clinical trials and real-world data; for example, it can be speculated that eyes with more ocular comorbidities are at increased risk of symptomatic IOP increase, intraocular inflammation, and retinal detachment.

There are several limitations to this study. First, the inconsistent reporting of eligibility criteria: RCTs vary in the detail with which they report eligibility criteria, which can introduce heterogeneity and affect the ability to perform direct comparisons across studies. Second, the risk of overgeneralization across diverse RCT designs. Third, the potential for misclassification of exclusion categories: when collating data from multiple studies, differences in terminology or varying definitions across RCTs could result in misclassification of eligibility criteria. This could introduce classification bias, impacting the accuracy of the analysis regarding how certain criteria affect study outcomes and external validity. Finally, there is also a limitation in that many RCTs focus on new drugs whereas real-world clinical practice to a large extent relies on off-label bevacizumab for nAMD.

In conclusion, this systematic review highlights that RCTs assessing intravitreal anti-VEGF treatments employ a number of eligibility criteria, which may lead to a homogeneous study population that do not fully represent the spectrum of patients seen in real-world clinical practice. As a result, these RCTs may not fully capture the diversity and complexity of real-world nAMD cases, potentially limiting the applicability of their findings to broader patient populations. Regularity agencies are increasingly expecting a more diverse study population to ensure that approval studies are generalizable for real-world settings[77], however, these initial strives are not expected to fully transform study populations to that of real-world practice. Hence, our study also highlights the importance of conducting real-world studies when understanding efficacy of anti-VEGF therapy in real-world patients with nAMD.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Lasse J. Cehofski reports a relationship with AbbVie Ltd. that includes: consulting or advisory and speaking and lecture fees. Lasse J. Cehofski reports a relationship with Bayer AG that includes: speaking and lecture fees. Lasse J. Cehofski reports a relationship with Novartis that includes: consulting or advisory. Lasse J. Cehofski reports a relationship with Roche that includes: consulting or advisory. Jakob Grauslund reports a relationship with Allergan Pharmaceuticals (Pty) Ltd that includes: consulting or advisory and speaking and lecture fees. Jakob Grauslund reports a relationship with Bayer AG that includes: consulting or advisory and speaking and lecture fees. Jakob Grauslund

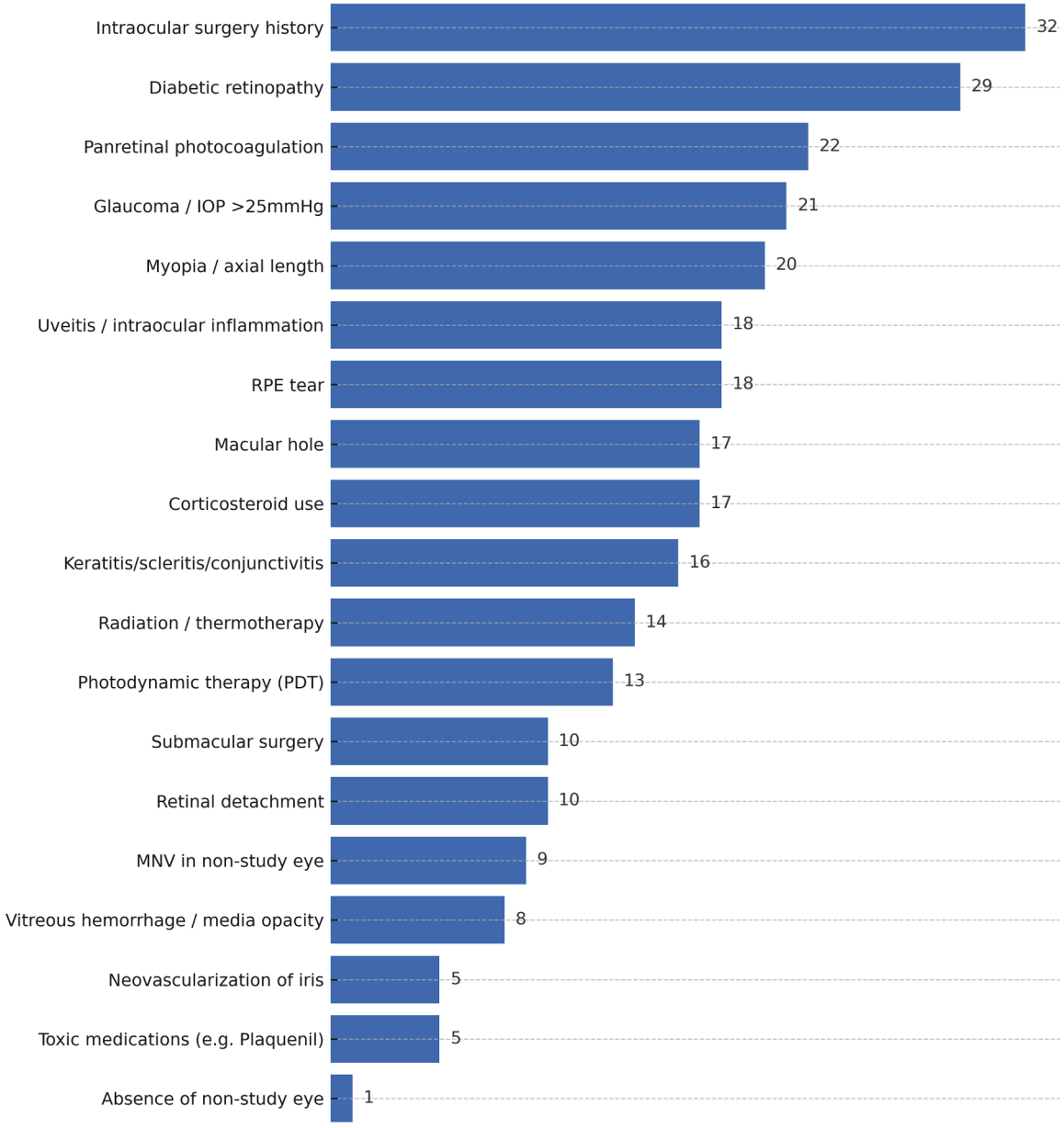

Fig. 2. Number of studies with exclusion criteria related to ocular comorbidities.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajoint.2025.100124.

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